VOLUME 93 • JANUARY 1957 • NUMBER 1

DISEASES OF CHILDREN

Presidential Address: Society for Pediatric Research

Wolf W. Zuelzer

The Society for Pediatric Research

Cholelithiasis Complicating Sickle-Cell Anemia

James G. Easton and Phyllis M. Wright

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A. M. A.
Journal of Diseases of Children

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The change in page format is confined to the title, subtitle, and authors' names. The change from a Coronet Bold type face to Bodoni Bold will eliminate the difficulty encountered when reading a formula or an abbreviation in script capitals. The use of Antique Italic for subtitles and Spartan Bold for the authors creates a desirable distinction between these parts. The arrangement realizes a saving in space.

This new cover is a development of an idea. It is not the result of a sudden thought. First, a suggestion was presented which was nothing more than a different arrangement of familiar elements. Then followed the collection of reactions, suggestions, and additional experimentation in search for the inspiration. All of the separate bits of information gathered were thoroughly digested, and the relationship between elements was established. The result is the crystallization of the idea. In following this procedure, our readers and editors have contributed immeasurably to the end product. Their cooperation means a new design of lasting quality.

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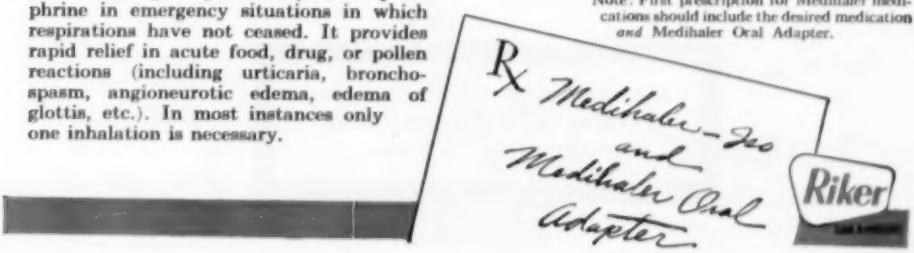

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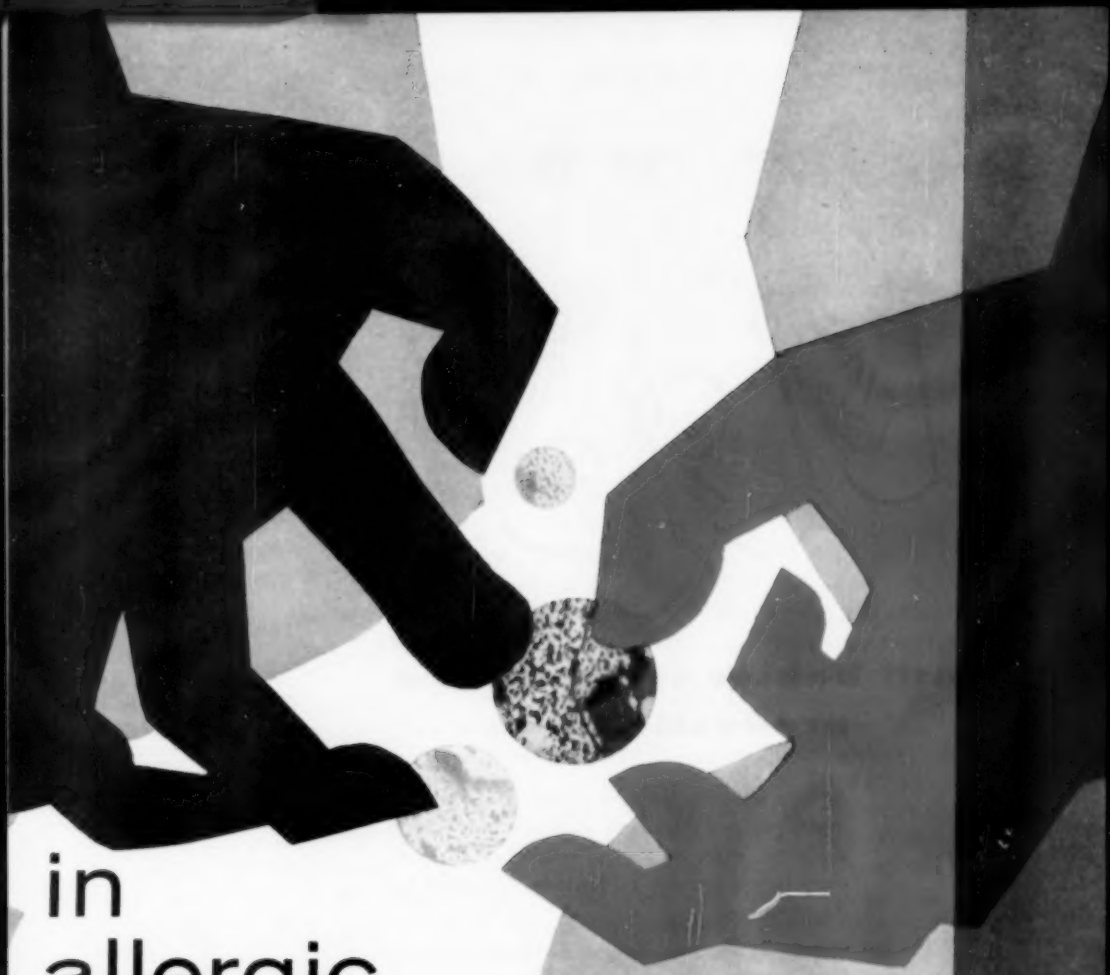

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A.M.A JOURNAL OF
DISEASES OF CHILDREN

Presidential Address
Society for Pediatric Research

WOLF W. ZUELZER, M.D., Detroit

Last year the special circumstance of holding our meeting jointly with the other pediatric societies prevented us from hearing my predecessor give his presidential address. Undoubtedly we were thus deprived of a great intellectual pleasure, but not only the members but also Dr. Janeway himself must have regretted this momentary lapse in our tradition. The presidential address affords the speaker the opportunity, and indeed serves him chiefly for the purpose, of acknowledging his debt of gratitude to the society. This is the one pleasure connected with the office which I for one should not like to forego. My predecessor, like all those before him, must have felt the desire to thank you for an honor which to my way of thinking is the highest form of recognition our endeavors can receive.

This urge for presidential self-expression is all the greater because by tradition the office is likely to be given to those who, like me, are about to be relegated to the limbo of emeritushood. The occasion thus becomes a parting, charged with more than a twinge of nostalgia. It is perhaps the first time in my career that I am forced to look backward. I am deeply grateful for the opportunities you have given me, the lessons learned, the friendships begun here, and as I reluctantly give up my active membership I feel a bit like the old-timer in the family firm who is called to the front office to receive his retirement papers and his engraved watch. Like him I can only say "thank you" and wish I could think of something more original.

I need hardly spell out wherein my debt to this society consists. Each of you by his presence indicates his awareness of the values to be had here. I should only like to name three things which particularly appeal to me about these meetings.

The first one is almost a by-product but an important ingredient just the same. If I weren't afraid of an overworked cliché I would call it the democratic spirit of this society. The only thing which counts here is the contribution a man has to make. The youngest investigator has the same opportunity as the established head of the department. In fact, professors have crept into the organization only because younger and younger men are being drafted into chairmanships. We need a new society which I propose to call the S. P. P. P.—The Society for the Protection of Potential Professors. As for us old-timers, any professorial pretenses or parochial attitudes which might have developed during a year spent in the protected recesses of our departments are quickly dispelled as we meet our equals and our betters; as we find that nimbler minds have already thought of the experiment which was only vaguely taking shape in ours; as our pet theories dissolve in the heat of a friendly argument at the bar—at

Submitted for publication June 22, 1956; accepted June 25.

Presented at Buck Hill Falls, Pa., May, 1956.

least when there *is* a bar. In some parts of the world where the habit of hierarchy is still strong and only bearded professors express opinions, the incentive for self-examination is lacking and ideas are exchanged less freely. Where the right to speak is the prerogative of the chair—an object notoriously associated with the least active part of the anatomy—the results are apt to be sedentary. This society, on the contrary, tends to keep us on our toes.

The second item on my list of things I have enjoyed as a member of the society is the intellectual climate. I have always been impressed with the courtesy of the discussions, and even more with the intellectual honesty of the speakers. The attitude here has always been: Let the data speak. Let's agree on our facts, and any differences of opinion will take care of themselves. There is very little fencing with words and no enmity because of apparent disagreement. A passage in the Religio Medici expresses this spirit perfectly: "I could never divide myself from any man upon the difference of an opinion, or be angry with his judgment for not agreeing with me on that from which perhaps within a few days I should dissent myself."

Men and women come before this society to give their best effort and in return to receive the best criticism. One does not try to make an impression. There is no room for self-advertisement, for publicity-seeking, for spectacular claims.

You may have taken all this for granted —these things after all form the credo of the scientist—and you may be surprised at my belaboring an obvious point. But the time may come when we will have reason to be grateful for the existence of societies such as this one. We live in the age of public relations and mass media, the age of the press release, the television show, the magazine article, the government contract, and the commercial sponsor. As the tools of research are becoming more expensive, as departments are growing larger and more complex, competition for funds and thus for publicity is creating dangerous pressures. There is always a temptation to let the ends justify the means. Already there is too much emphasis on what we might call the utilitarian aspects of medical research, on practical application rather than theoretical implication; too much dramatization of results, too much confusion between technologic and intellectual achievement.

Now medical research has a split personality. Part of it must always be frankly utilitarian. As physicians we are primarily interested in disease because we are looking for cures and prevention. I am not questioning the need for support from nonacademic sources, nor do I doubt that in the society we live in the scientist must leave the ivory tower and acquaint the public with both his aims and his achievements. But he must guard against paying too heavy a tribute. He dare not sacrifice his scientific integrity. The other half of his split personality, the part that seeks to understand biologic phenomena regardless of their practical importance must retain the upper hand in his thinking habits. And as long as he must bring his work to a forum such as this to be appraised by his friends and peers, as long as it remains his ambition to receive our criticism rather than the engineered acclaim of the public, any serious confusion of aims and values is unlikely.

I am tempted to go on and talk for a minute about the counterpart of this problem in lay circles. Lately, with our tacit or active support a trend has developed among the public at large which cannot help but influence the pattern of research. I am speaking of the phenomenon of sponsoring specific and often narrowly defined diseases as objects of fund-raising. The initiative often arises from laymen, and the motives, if not the thinking, are usually of the best. To be sure, there are some undertakings of this sort in which research is merely a pious and convenient front concealing the profits of professional fund raisers, in short a form of charity racketeering.

I shan't dwell on these obvious and easily unmasked abuses. My concern is with the subtler and more difficult problem posed by

Figure 1

the honest and sincere donor. Sponsorship of specific medical causes by lay groups or individuals is really a new phenomenon insofar as it aims no longer solely at charity or direct help for those suffering from a particular disease but at supporting or even creating research in a specific and restricted area chosen by the donor. The shift has occurred so quickly that the public at least seems hardly aware of the distinction. But through it the emotional motivation of the donor and his understanding of the scientific method are rapidly becoming important factors in medical research.

I have done a little research myself on the subject of donors in an unrelated but nonetheless illuminating field, the history of art, and uncovered an interesting parallel. In early medieval altar paintings one often sees the donor represented as a small inconspicuous figure devoutly kneeling in a corner of the picture. The proportions express his relationship to the artist and his subject. Clearly it is his role to help but in no way to dominate or dictate the design. This attitude is illustrated in the charming painting of the Madonna by an unknown artist of the early 14th century (Fig. 1). But slowly we see the donor move farther and farther into the foreground and into the center of the picture. In this triptych by Van Eyck the donor has already reached larger proportions but he is still not in the center and he is still overshadowed by the archangel who seems to guide him and point out to him the object of his worship (Fig. 2). But the same artist in another painting (Fig. 3), using all the skills of the portrait painter, depicts the donor quite conspicuously in great detail. In this magnificent portrait the donor, though kneeling, nevertheless seems to dominate the picture, and one gets the impression that

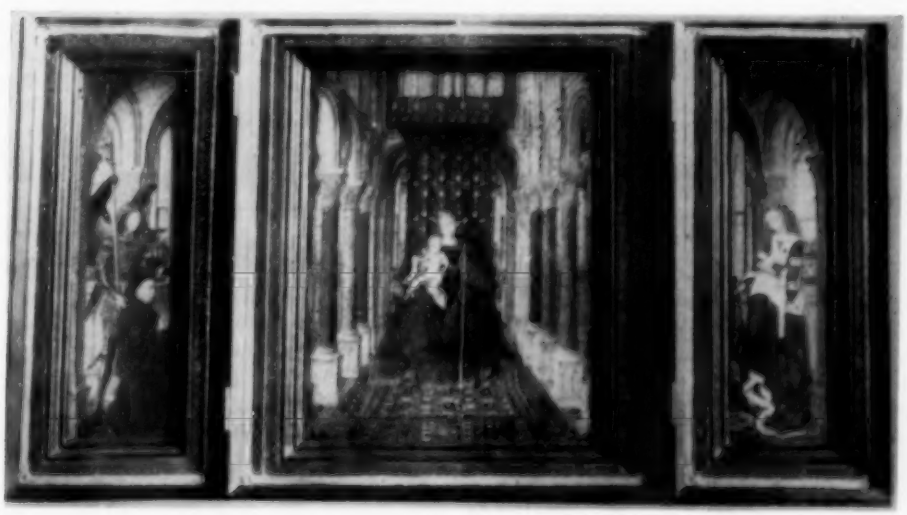

Figure 2

Figure 3

this square-jawed and determined-looking gentleman had his somewhat suspicious eye on the progress of the painting and would let the artist know if a brush stroke were not to his liking. In Holbein's "Burgomaster" Madonna, the process is already completed (Fig. 4). In this famous painting the Madonna is scarcely more than a pretext for a delightful family portrait and the donor's grandchild competes successfully with the Christ Child for the attention of the beholder.

Figure 4

The parallel is obvious. The modern donor worshipping at the shrine of science looms larger and larger in the contemporary picture. Like his medieval counterpart he too may not be content simply to bring his gift but may want to prescribe both the subject and the execution.

Basically the interest of the layman in research is of course welcome and wholesome. In the long run funds are more fruitfully spent if applied to investigation than to patient care, provided that their use is not too narrowly circumscribed, provided that the investigator is not tied too closely to a particular subject and thus prevented from exercising his freedom of inquiry. It is our responsibility to guide and enlighten the donor in this respect. But even so, the pattern now developing with the creation, almost week by week, of new foundations devoted nominally at least, to single diseases deviates from the catholic nature of science, threatens the cherished principle of serendipity, atomizes the academic unity of research. It distorts the normal processes of investigation by placing a premium on topics which happen to have—or can be engineered to have—popular appeal. Indirectly it thus penalizes research which does not happen to be of obvious public interest. The donor who by his contribution attempts to channel our

efforts in this or that direction unwittingly arrogates unto himself a function which belongs to the scientific community itself.

How productive this influence can be remains to be seen. I need not point out that the enthusiastic donor frequently labors under the misconception that money can produce ideas and further that a medical problem can be solved by frontal attack. He is likely to think in terms of "discovery" and "break-through," "fighting disease" and "routing the enemy," analogies borrowed from the military, which, I am sorry to say, some of our colleagues have been also using but which are of course not in the least descriptive of the kinetics of medical progress. You may object that understanding is not essential so long as the funds are forthcoming. As the music master says to the dancing master while they are waiting for their *nouveau riche* employer in Moliere's comedy: "If only those supported us who can truly appreciate our art we should both starve to death." Nevertheless, the intelligent appreciation of the processes involved in research seems to me essential if academic science and academic freedom are to survive.

An interesting by-product of the trend toward isolated causes is the competition developing among the sponsors themselves. Every lay group and foundation dealing with a particular disease rightly feels that it has a worthy cause. The devotion of the members to this cause often is a very fine and unselfish thing. Not infrequently it even has therapeutic value in providing an outlet for the energies and emotions of tragically frustrated people. But sooner or later in the perspective of the layman the true identity of purpose of the various worthy causes is no longer apparent, and a highly competitive spirit develops. Soon such organizations are driven to advertising methods in attempting to raise funds. Soon the contemporary disease of bigness overtakes them and they attempt to "go national" whether it makes any sense or not. The town, the state, and the country is blanketed with appeals. Appeals must be engineered by mass media. The professional entertainer, the columnist, and the politician are enlisted. They are "sold" on the merits of this or that disease and in turn become decisive factors by selling it to the public as a particularly worthy cause. Actually it becomes merchandise, and the process results in popularity contests between diseases. "More fatal cases than any other brand."

But how is the public to choose? Is leukemia more tragic than nephrosis? Are there more sufferers from multiple sclerosis than from muscular dystrophy? Is fibrocystic disease to be preferred over familial dysautonomia? Were Betty Hutton's tears more convincing than Martha Raye's sobs? Are we celebrating arthritis week, internal hydrocephalus day, or congenital atresia-of-the-bile-ducts month? One may hope that public saturation with the plethora of isolated causes, hastened perhaps by sheer inability to choose, will arrest this trend and bring back a pattern of support for research as a whole, an indivisible entity wherein the free interplay of ideas will produce progress at its own pace. It seems safe to say that more would be accomplished though perhaps far less money would be raised if all these well-meaning donors, recognizing the identity of their interest would pool their efforts on behalf of a single, broadly conceived research fund or, better yet, of medical schools in general. Such a trend will not come by itself or by a few voices crying in the wilderness. Nor will it suffice to acquaint the public with the acute technical problems which confront us. It is a permanent job for all of us to help educate our lay friends to the realities of science. I for one believe that this task is second in importance only to our work itself.

This is a moment when one is permitted to indulge in some personal remarks. To quote Samuel Butler: "Every man's work, whether it be literature or music or pictures or architecture or anything else, is always a portrait of himself, and the more he tries to conceal himself the more clearly will his character appear in spite of him." It would do me no good then to try to hide from you the fact that where medical research is con-

cerned, I am an eclectic, or worse, an opportunist. I admit to having yielded to intellectual temptation on more than one occasion and to have picked such flowers as I have been able to find in more than one garden. My only excuse is that I don't believe in fences.

If in electing me to this office you have endorsed this attitude then I am indeed deeply pleased, because the third and to me most precious attribute of this society is its eclectic and encyclopedic spirit. The bond that holds it together is not the identity of method or even the common interest but, on the contrary, the difference and the diversity of interests. As it becomes more difficult for all of us to maintain communication and perspective, this society becomes ever more important, for we must continue to talk to one another or we shall end up talking to ourselves.

The increasing complexity of the tools we use is bound to circumscribe our visual fields, force each of us to tend a narrower plot. Perhaps the future belongs to those who wisely limit themselves and master the intricacies of one method. We owe more and more to those who set themselves fixed goals and pursue a single problem to its final solution. The trend of the time is certainly in that direction whether we like it or not. Even a Benjamin Franklin might find the going rough in the second half of the twentieth century. But specialism is only a necessary evil, not at all desirable in itself. The encyclopedic viewpoint, the exercise of universal curiosity remains legitimate. If anything, the need for synthesis is growing, though the time may be far when it can be accomplished. In the meantime, if we can't all speak the same language, each of us must at least be able to understand several different languages and even if, as I am told, the "electrolyte boys" are tempted to sneak out while the virologist is speaking and vice versa, let us keep talking to each other.

Society Transactions

THE SOCIETY FOR PEDIATRIC RESEARCH

Twenty-Sixth Annual Meeting, Buck Hill Falls, Pa., May 7 and 8, 1956

The Indirect Effect of Irradiation on Rat Embryos. ROBERT L. BRENT,* Walter Reed. (Introduced by Gilbert Forbes)

The etiology of congenital malformations is a subject into which only a few inroads have been made. Even in the few cases where agents or environmental conditions are known to be causative, the basic mechanism is still puzzling.

In the past few years a number of workers have produced congenital malformations in mammals with the use of ionizing radiation, (Warkany, Kaven, Hicks, Russel, Rugh, Wilson, and Brent). Except for the experiments of Wilson and Brent, both the maternal organism and the embryos were irradiated, while in their studies only the embryos were irradiated. It had been assumed that all the malformations observed were due to the direct effect of irradiating the embryos and that the radiation effect in the mother played no part in inducing malformations. Wilson and Brent seemed to corroborate these assumptions, since they obtained a similar spectrum of malformations even though they irradiated only the embryos. Because of this inconclusive evidence, it was felt that the following experiment would clarify this problem.

Using a 250 kv. x-ray machine, (30 ma. filter 1 mm. Cu and Al, 50 cm. T. O. D.) Wistar rats, pregnant nine days, were given 400 r, while the entire litter was shielded with lead so that the embryos received less than 0.5 r. The rats were anesthetized, and a laparotomy enabled one to visualize and shield the embryos.

Controls were operated upon and shielded for the same length of time as the experimental animals. The animals were allowed to survive for 12 days and were killed 24 hours before delivery to observe the fetuses.

The reason the ninth gestational day was chosen for irradiation is that it proved to be the most sensitive day for malformation production, yielding many easily observable malformations of the brain, eye, and face. As little as 50 r resulted in severe malformation and 200 r was uniformly fatal.

Three hundred ninety-four embryos in 40 pregnant rats have been studied and in none of the radiated or controls were there any of the malformations previously associated with this stage in gestation; nor were any new malformations uncovered. The weights of the fetuses from the irradiated and the unirradiated mothers did not differ significantly in the survivors.

Of the control embryos (operated, shielded, but not irradiated) 10% resorbed, a figure not much higher than the normal resorption rate of 9-day-old rat embryos. The over-all resorption rate in the maternally-irradiated litters was 33%, but this is misleading, since only 5 of the 27 experimental animals had resorption rates greater than the controls. If these five animals were left out of the series, the control and experimental litters would have the same resorption rates.

This would indicate that all the metabolic derangements that are produced in the radiation syndrome in the maternal animals (1) have no effect on the birth weight of the fetus, (2) produces none of the grossly observable malformations associated with irradiation of the 9-day-old embryos, (3) does not increase the resorption rate in most of the experimental animals but does cause 100% resorption in only a few of the litters. This mirrors a result that one commonly sees clinically, in that if the maternal organism becomes sick enough the pregnancy will be halted but if carried to term the fetus may be normal.

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* By Invitation

DISCUSSION

DR. JOSEF WARKANY, Cincinnati: This paper is clear cut and does not require much discussion. Dr. Brent should be commended for his work which shows that teratologic problems can be approached quantitatively.

Although he did not discuss irradiation of human beings, I should like to ask him whether irradiation of women in early pregnancy could lead to damage to the embryo, although the x-rays do not reach directly the uterus containing the embryos?

DR. ROBERT L. BRENT: The data that stimulated this work was, as I said, the spotty evidence presented in the literature that low doses of radiation to nonproductive areas of pregnant women might result in a congenitally malformed child. Individual cases have reported congenital malformation following a chest x-ray late in pregnancy.

Whether indirect irradiation can produce congenital malformation in the human is not yet answered. We observe no malformation with low doses, but in humans much larger doses of local irradiation would be used, i. e., the treatment of Hodgkin's disease or lymphosarcoma of the neck,

etc. With low dosages there were no changes in the fetus. With higher doses there may be a chance that the fetus would be affected, for severe hematologic changes, metabolic and endocrine changes may occur, thus preventing the maternal environment from protecting the fetus from injury. At least we can say that with a low indirect dose fetal damage in the human is very unlikely.

The Transport of Amino Acids and Plasma Proteins Across the Placenta in the Guinea Pig. JOSEPH DANCIS, MANYA SHAFRON,* and WILLIAM L. MONEY,* N. Y. U.—Bellevue Medical Center and Sloan Kettering Institute.

An investigation was made into the materials which the fetal guinea pig derives from the mother for the synthesis of proteins. Guinea pig placenta is similar histologically to human placenta.

1. (a) S^{35} methionine was injected into newborn guinea pigs and fetal guinea pigs delivered by hysterotomy the last week of gestation. This demonstrated that the fetus was capable of synthesizing from amino acids tissue proteins and all fractions of plasma proteins identifiable by zone electrophoresis except for γ globulin.

(b) Injection of S^{35} methionine intravenously into the pregnant guinea pig demonstrated that amino acids rapidly cross the placenta where they can be utilized by the fetus.

2. Radioactive plasma proteins prepared biosynthetically were injected into pregnant guinea pigs. Twenty-four hours later the fetuses were delivered by hysterotomy. Fetal plasma was fractionated by zone electrophoresis and radioactivity was found in all fractions of the plasma proteins. There was also incorporation of radioactivity into fetal tissue.

3. Radioactive plasma proteins from donor guinea pigs were fractionated by zone electrophoresis and the γ globulin fraction injected into pregnant guinea pigs. Radioactivity was found in the gamma globulin fraction and the immediately adjacent fraction in the fetus but not in other fractions. When radioactive β globulin was injected, the radioactivity was found in the fetal β globulin and adjacent zones but not elsewhere. Apparently the placenta does not appreciably degrade these proteins for resynthesis by the fetus.

4. Tissue slices from placenta, maternal and fetal liver were incubated with radioactive plasma proteins. Similar amounts of radioactivity were released from the plasma proteins by each tissue indicating that the placenta does not have unusual proteolytic activity.

Conclusions.—The fetus in utero is capable of using maternal amino acids for the synthesis of tissue proteins and all plasma proteins except gamma globulin. All plasma proteins identifiable by zone electrophoresis are able to cross the placenta from the maternal circulation into the fetal circulation, where they may serve as plasma proteins or be incorporated into tissue proteins. There does not appear to be significant degradation of maternal plasma proteins by the placenta to provide materials for fetal use.

DISCUSSION

DR. CHARLES A. JANEWAY, Boston: May emeritus members speak? I'd just like to congratulate Dr. Dancis on doing what I believe is a beautiful job. I had the pleasure of hearing Dr. Dancis talk about what he was going to do before he started a few years ago and then of watching this steady flow of nice work on the relation of the placenta to plasma and tissue protein synthesis by the fetus.

It's worth pointing out that what Dr. Dancis has demonstrated so nicely here by dynamic studies fits in with the work which has been done on a more descriptive level with other methods. Dr. Martin, in England, has studied human fetuses and shown no evidence of the presence of gamma globulin in the plasma proteins of the human embryo before about 22 weeks of gestation, and a rise thereafter. This fits in with work of other people at New York University that, in premature babies, the level of gamma globulin is lower than it is in full-term babies.

This also fits in with the very nice job done in Toronto and reported to this Society several years ago by Dr. Sass-Kortsak and his colleagues, showing that the gamma globulin of the fetus tends to approximate that of the mother. Dr Slater, I believe, demonstrated that in one mother with a very high gamma globulin level, hypergammaglobulinemia likewise was present in the newborn infant. The studies of Sass-Kortsak and others showed that the disappearance of gamma globulin from the circulation of the newborn child goes at a rate which is comparable to the normal half-life of gamma globulin.

When all this is put together we get a pretty clear picture that gamma globulin is not formed in utero by the fetus and that gamma globulin is not formed in the first month of life after birth under normal circumstances but that starting at about 4 to 5 weeks of age gamma globulin synthesis by the newborn infant begins to get under way, and this fits with the older studies on poorer antibody formation in the earliest period of life.

It's interesting that gamma globulin synthesis and metabolism seems to be sequestered, so to speak, from the metabolism of the rest of the proteins, and Dr. Gitlin has indicated that under conditions of starvation and inadequate supplies of calories and protein gamma globulin is protected, so to speak, from the catabolic processes that affect other plasma proteins.

LYTT I. GARDNER, Syracuse, N. Y.: The paper by Dr. Dancis and colleagues also relates very nicely to some of the more recent findings in connection with 17-OH-corticosteroid hormone concentrations in the plasma of fetuses. Gemzell and colleagues (*Acta endocrinol.* 17:100, 1954) and Migeon and colleagues (*J. Clin. Invest.* 35:488, 1956) have recently shown that 17-OH-corticosteroid concentrations in human fetal plasma are minimal. Dr. Evelyn Howard at Hopkins has reported this spring studies indicating that dehydroepiandrosterone (DHA) (a weak androgen) competes in certain specialized ways with corticosterone (*Fed. Proc.* 15:97, 1956). Her experiments suggest that the normal growth of some tissues related to the sexual apparatus may be conditioned by the checks and balances of DHA vs. the corticoids. The DHA promotes protein anabolism, whereas the corticoids are antianabolic. Howard has found this system to be true for the growth of uterine and certain related tissues, but not for all body tissues. Hence in the human fetus, whose plasma has "high" concentrations of DHA and nearly absent corticoids, the setting is ideal for anabolism and embryologic development of the sexual apparatus à la Howard's scheme. After birth the "high" plasma DHA levels disappear, the plasma corticoids rise, and development of the sexual apparatus becomes quiescent until adolescence.

DR. ROBERT L. BRENT, Walter Reed Hospital: We have done some studies on serum proteins in embryos, and I'd like Dr. Dancis to comment on his method for drawing bloods, because we found it very important to draw a clean sample and make sure that no tissue proteins were included in the sample.

Secondly, since the guinea pig develops so rapidly, were all the studies done on the day before delivery or did you examine embryos of different ages? Placental function varies from day to day and it might not be correct to pool results from different gestational days.

DR. JOSEPH DANCIS: Because of the need for sufficient volumes of blood for electrophoretic separations of plasma proteins, the experiments were done with guinea pigs close to term. The fetuses were large and had hair. The exact duration of gestation was not known.

Our major concern in collecting fetal samples was contamination by maternal blood, and that is solved by operative technique. Contamination by tissue protein worried us little. As can be seen from the results, relatively large amounts of contamination, far more than can be properly expected from the tissues, could be tolerated without influencing the interpretation.

Measurements of Fetal Hemoglobin in Newborn Infants: Correlation with Gestational Age and Placental Insufficiency. C. D. COOK, H. R. BRODIE,* and D. W. ALLEN,* Harvard.

The presence of fetal hemoglobin in newborn infants has been recognized for many years and previous authors have demonstrated a difference between the per cent of fetal hemoglobin in premature and full-term infants. However, with the techniques for measurement employed, no relation between the per cent of fetal hemoglobin present at birth and the gestational age could be demonstrated within the premature and full-term groups. The present study was undertaken, using the alkali denaturization curve technique described by Jonxis, to study more exactly the relation between fetal hemoglobin and gestational age. In addition the relation between fetal and total hemoglobin concentrations and estimated total body hemoglobin and the presence or absence of intrauterine asphyxia was studied. In all, blood from 144 infants ranging in estimated gestational age from 25 to 44 weeks was examined. Of these infants 28 were considered to have had prenatal asphyxia, as evidenced by striking meconium staining of the skin, fingernails, and umbilical cord. In many of these the complete picture of post-maturity and placental insufficiency as described by Clifford was present.

All but 2 of the 27 infants of less than 36 weeks' gestation had more than 90% fetal hemoglobin at birth. All but 3 of the 117 infants of 36 weeks' or more gestation had less than 90% fetal hemoglobin. In infants of more than 34 weeks' gestation there was found to be an inverse relation between gestational age and per cent of fetal hemoglobin, the fetal hemoglobin concentration found at birth being less by approximately 4% for each two-week increment in gestational age. Average values of 91% (range 81%-93%) for infants of 34 to 36 weeks' gestation and 72% (range 55%-83%) for infants between 42 and 44 weeks' gestation were found. As is apparent from the ranges shown, there was considerable spread of the values in each gestational age group, presumably due to biological variation and errors related to estimation of gestational age.

Certain authors have suggested that postmaturity associated with placental insufficiency and intrauterine anoxia leads to increased production of hemoglobin, particularly fetal. While the total hemoglobin concentrations in the asphyxiated postmature group were slightly greater than the nonasphyxiated group, the per cent of fetal hemoglobin was found to be decreased. Calculations of total body fetal hemoglobin suggest that there is little difference between the asphyxiated and nonasphyxiated infants of the same gestational age. In 47 of the infants the reticulocyte concentrations were studied and there was an indirect relation to gesta-

tional age but no relation to the presence or absence of evidence of intrauterine distress. These data therefore suggest that intrauterine anoxia of the sort observed particularly in postmature infants does not necessarily produce an increase in red-cell or hemoglobin production and that the increased concentrations of total hemoglobins observed in these infants may only be a result of dehydration and hemoconcentration, a possibility also suggested by clinical examination.

The Occurrence of Anemia of the Newborn in Association with the Appearance of Fetal Hemoglobin in the Maternal Circulation. WALTER J. O'CONNOR,* GEORGE SHIELDS,* SCHUYLER KOHL,* and MARVIN SUSSMAN,* State University of N. Y., Brooklyn. (Introduced by Richard Day)

The object of the study has been to search for examples of fetal hemorrhage into maternal circulation, as reported in three instances by Dr. Bruce Chown in 1954.

Since the determination of fetal hemoglobin at concentrations of less than 10% is subject to error, we sought to ascertain the reliability of the method. Mixtures of cord and adult blood were made and tested by a modification of the method of Ponder. The results indicated to us that percentages of fetal hemoglobin less than 1 could be distinguished from amounts equalling 2% or more. In the study results indicating 1% or less were arbitrarily labelled "negative" and those indicating more were labelled "positive."

Postpartum bloods were drawn from 42 mothers. Twenty-nine of these women served as controls and were picked at random. Of the 29 specimens, 28 were "negative" for fetal hemoglobin. The blood of another group of women was tested because their infants looked pale or were anemic. Thirteen such women were found whose bloods were "positive" for fetal hemoglobin. These, together with the "positive" specimen found among the control women made a series of 14 instances in which fetal hemoglobin was thought to have been found in the maternal circulation.

The 14 infants born to the "positive" women had hemoglobins ranging from 10 to 23 gm., with an average of 14.9 gm. The infants of the 28 "negative" women had an average hemoglobin value of 18.2 gm., with a range of from 15 to 24 gm. Analysis showed that a mean difference between the two groups as great as that found would occur by chance less than one time in 100.

Of the 14 infants born to "positive" women, one was seriously ill, and transfusion was thought to be needed to avoid shock. Another may have suffered from erythroblastosis due to incompatibility of the A blood group factor. There were two sets of twins. In addition, six women delivering stillborn infants were tested; one had peripheral blood "positive" for fetal hemoglobin and two had "positive" blood issuing from the cervix.

The search for pale infants, considered worthy of hemoglobin determinations and maternal testing, was made in the nursery during a period when less than 3000 infants were born.

It is concluded that the association of some degree of anemia of the newborn and the appearance of fetal hemoglobin in the maternal circulation is not uncommon. Since in every instance the fetal hemoglobin diseappeared from the maternal blood within three months postpartum, pregnancy must in some way be related to the phenomenon. Either maternal stress or fetal hemorrhage into the maternal circulation could be postulated to explain the observed results. The authors favor the latter view because the infants' clinical course in some instances suggested a recent hemorrhage.

DISCUSSION

DR. IRVING SCHULMAN, New York: I was very much interested in both of these papers and should like to commend both groups of workers.

Dr. Cook's results are particularly gratifying because we were becoming somewhat concerned about recent reports which suggested that fetal hemoglobin production could be recalled in response to hypoxia. Such observations were at variance with those which indicated that once the baby begins to make adult hemoglobin he continues to do so unless an aberration of the hematopoietic system itself exists. Certainly in children with hypoxia secondary to cyanotic heart disease fetal hemoglobin remains at normal levels. The data presented by Dr. Cook have direct bearing on Dr. O'Connor's paper because it indicates that the fetal hemoglobin found in the mother is, in all probability, of fetal origin.

DR. JOSEPH DANCIS, New York: I'd like to raise a point in relation to Dr. Cook's paper.

We have recently studied the osmotic relations on both sides of the placenta of the pregnant rabbit, and we found they paralleled each other both under normal and abnormal circumstances. Because of this, I find it difficult to understand how dehydration can exist in the newborn infant in the absence of dehydration in the mother, if by dehydration is meant a deficiency in water with a resultant increase in osmotic pressure.

DR. BERNARD LASKI, Toronto: In 1954, at the same time Dr. Chown presented his paper, we presented 22 cases of this syndrome which has been called nonhemolytic anemia of the newborn. At that time, we had been unable to prove that these cases were due to hemorrhage from the baby into the mother, but we postulated this hypothesis.

Since then, we have been able to demonstrate in several cases in our laboratory fetal cells and fetal hemoglobin in the mother, and it is very

gratifying that others are now accepting and proving this hypothesis. I believe this condition occurs much more frequently than is realized, and if the obstetricians or pediatricians would do hemoglobin tests routinely on all newborns it would be picked up much more frequently.

I believe these children are protected, because we have found that those children whose hemoglobins are in the neighborhood of 11 to 12 gm. usually need no treatment, since their hemoglobins fall no further and usually rise rapidly. I feel that treatment or transfusion is necessary only in those children whose hemoglobin falls below 8 or 9 gm. or who show evidence of shock.

DR. BRUCE CHOWN, Winnipeg: Mr. Chairman, there's only one question I'd like to raise.

In the abstract of Dr. O'Connor's paper, he refers to one child who was Group A, and the mother Group O. I should be very surprised to find fetal hemoglobin derived from a baby in the circulation of the mother under such circumstances, and that one observation, unless there is something further to clarify it, makes me just a little doubtful about this method of proving fetal bleeding into the maternal circulation.

We have looked for this condition not too intensively in the last two years without seeing any further cases that we could prove, although there were some we thought probably were of this nature.

PRESIDENT ZUELZER: I should like to ask a question or two myself of Dr. Cook.

Was the hemoglobin level on the infant obtained from the cord or from the heel, and was there any reason to think that the asphyxia was of any duration, or was this an acute episode, as far as the history would go?

I'll ask Dr. Cook and Dr. O'Connor both to close the discussion.

DR. C. D. COOK, Boston: In answer to Dr. Dancis' comment about dehydration in these infants, I can only say that the diagnosis of dehydration has been made entirely on clinical grounds. In addition, however, examination of the postmature placenta suggests an abnormal organ and one which might be associated with nutritional failure and improper fluid balance. Certainly, final conclusions await blood volume and total body water measurements on these postmature infants.

In answer to Dr. Zuelzer's question concerning blood sampling techniques, blood was obtained from both cord and capillary blood. We realized the limitations of blood sampling in newborns for accurate hemoglobin determinations. However, since a relatively large number of determinations (75) were done, the difference between the postmature infants with asphyxia and those without asphyxia appeared significant.

Concerning the duration of the anoxia, we have no definite idea as to the duration, since it was intrauterine. The infants seemed to have wasting in most cases, and severe meconium staining of the fingernails, cord, and skin, and we therefore presumed that the duration of the anoxia was at least of several days', if not weeks', duration.

DR. WALTER J. O'CONNOR, Brooklyn: There is a misstatement in the published abstract. One baby who had 23 gm. of hemoglobin at birth is included as an example of fetal hemorrhage. Since this mother to date has not been available for follow-up study, the infant should not be included in the present series of cases.

In answer to the question regarding incompatibility of blood groups—three of the mothers were type O while the infants were type A or B. However, I don't recall the time between delivery and the withdrawing of maternal blood to test for fetal hemoglobin. Certainly the time interval may be a great factor in the ability to detect fetal hemoglobin in such cases.

Electron Microscopy of Newborn Infant Lungs (Preliminary Report). WILLIAM T. NEWSOM,* Charity Hospital, New Orleans. (Introduced by R. V. Platou)

Satisfactory visualization of the pulmonary alveolar epithelium in the mammalian lung is extremely difficult using routine pathological techniques of fixation and the light microscope. Using the special techniques of fixation and preparation of fresh tissue for electron microscopy, the lungs of infants of various weight groups, particularly prematures, who died from various causes have been examined by this technique. Slides will be shown to illustrate the existence of this epithelial lining and comparisons will be made with findings commonly observed by usual pathological techniques. As of this abstract date, none of the infants studied had hyaline membranes demonstrated by conventional necropsies.

DR. JOHN M. CRAIG, Boston: I have seen similar photographs prepared on the electron microscope by Bruns and Shields, of Colorado. They were able to demonstrate the presence of fibrin in hyaline membranes, identifying it by its characteristic periodicity. This was very gratifying to Dr. Gitlin and myself in that by the Coons labeling fluorescent technique we have shown a large amount of fibrin to be present within the hyaline membranes.

Gas Diffusion and Pulmonary Ventilation in the Newborn. MILDRED STAHLMAN,* Vanderbilt. (Introduced by Amos Christie)

The problem of the direct measurement of gas diffusion across the pulmonary alveolar-capillary membrane has not been approached in small infants. Also, because of the problems of dead space and resistance, indirect methods such as the body plethysmograph, have been used to measure the ven-

tilatory aspects of the lung in the newborn infant. Direct measurements of diffusion and ventilation should be useful in delineating the physiological defect in the different types of respiratory distress in the newborn, such as in "hyaline membrane" disease. The Filley "steady-state" carbon monoxide method of measuring the diffusion properties of the lung has been modified for use in small infants, utilizing a system which also gives direct measurements of ventilation. The diffusion capacity for a given gas is defined as that quantity of gas transferred each minute for each millimeter of mercury difference in partial pressure of that gas across the alveolar-capillary membrane. Since carbon monoxide when breathed in low concentrations (0.1-0.2%) combines so readily with hemoglobin, the mean effective pulmonary capillary partial pressure of carbon monoxide can be kept effectively zero and ignored as a measurement in this method. The method, therefore, requires only a knowledge of carbon monoxide uptake per minute and the alveolar partial pressure of carbon monoxide.

In order to keep the apparatus dead space and resistance to expiration at a minimum, a double Donald-Christie box arrangement was chosen with a 500-ml. counterbalanced spirometer interposed between the boxes. A small plastic contour mask was interposed between the two neoprene bags with small, low-resistance "J" valves on the inspired and expired sides. With this system, carbon monoxide uptake can be measured as well as all the usual ventilatory measurements. The alveolar partial pressure of carbon monoxide can be obtained from the measurement of the arterial tension of CO_2, the expired tension of CO_2, and the inspired and expired concentration of carbon monoxide. Direct measurements of the carbon monoxide diffusion capacity and pulmonary ventilation were made using this system in 32 normal newborn infants ranging in age from 9 hours to 8 days with a mean age of 40 hours. They varied in weight from 4 to 9 lb. For purposes of comparison, the same ventilation and diffusion measurements were carried out on 12 older children and normal adults of varying body size. The diffusion capacity of carbon monoxide, CO uptake, O_2 uptake, CO_2 output, minute ventilation, and alveolar ventilation are shown to increase with increased body size. Carbon monoxide uptake and oxygen uptake are shown to correlate well with alveolar ventilation in both the infants and adults studied, and carbon monoxide uptake correlates with oxygen uptake in both infants and adults.

DISCUSSION

DR. CLEMENT SMITH, Boston: I realize that Dr. Stahlman is a very cautious and very careful worker and will probably refuse to make any public answer to such a question, but I can't resist asking her whether the few babies of 9 hours are any different thus far in the course of her studies with this technique than the ones of 7 or 8 days. Anything that she could say about differences related to the age of the infants would of course only be very tentative.

DR. STAHLMAN: We have plotted all of our data, both ventilatory and diffusion measurements, against age in hours, and there does not seem to be any difference with increments in age. Body weight seems to be the best correlating factor.

Physiological Studies on the Cardiovascular Status of the Normal Newborn Infant (With Special Reference to the Ductus Arteriosus).

FORREST H. ADAMS and JOHN LIND,* Wenner-Gren Cardio-Vascular Research Laboratory and Univ. California at Los Angeles.

Although extensive studies have been performed on the cardiovascular status of newborn animals by Barclay, Barcoft, Dawes, and others, relatively little information is available on the newborn infant. These studies report the results obtained in normal newborn infants under 2 weeks of age by cardiac catheterization, electrocardiography, and heart volume determinations. In some instances the cardiac catheterization was performed within the first few hours after birth. Of special interest was the finding of pulmonary hypertension beyond the first few hours of life in association with patency of the ductus arteriosus. These data tend to confirm the recent observations made by Dawes in newborn lambs, and add support to his thesis that the ductus arteriosus needs to remain patent after birth at least for several hours or days.

The Pattern of Response of Pulmonary and Systemic Arterial Pressures in Newborn and Older Infants to Short Periods of Hypoxia.

RICHARD D. ROWE* and L. S. JAMES,* Toronto. (Introduced by John D. Keith)

Measurement of right heart, pulmonary artery, and systemic artery pressures were obtained in 12 infant Mongols in the course of a study to establish the incidence of congenital heart disease in this condition. In addition the effect on the circulatory dynamics of breathing an atmosphere of 10% oxygen was studied during the catheterization.

The average age of the older group of eight, who had no cardiac malformation, was 5 months, while the younger group of four, all of whom showed some evidence of incomplete adjustment to the adult type of circulation with the presence of either a probe-patent foramen ovale or a patent ductus arteriosus at catheterization, had an average age of 7 days.

The older group with an average mean resting pulmonary arterial pressure of 16 mm. Hg responded to short periods of hypoxia in a manner

similar to adults but the systemic arterial oxygen saturation fell to lower levels (56%) and the pulmonary artery pressure rises were greater (40 to 60% increase).

The newborn group with an average mean resting pulmonary arterial pressure of 42 mm. Hg showed smaller increases in pulmonary arterial pressure with hypoxia. This was associated with a rise in venous pressure, fall in systemic pressure, and a marked fall in systemic arterial oxygen saturation (av. 33% in 2 minutes). The change in the pressure relationships of the two circulations was such as to favor the reestablishment of a right-to-left shunt through the foramen ovale or the ductus arteriosus. One hundred per cent oxygen gave a rapid reversal to the adult type of circulation. In one case there was angiocardiographic evidence that the ductus arteriosus reopened during the period of induced hypoxia.

DISCUSSION

DR. CLEMENT SMITH, Boston: I should like to ask about the absence of a murmur in the cases studied by Dr. Adams and Dr. Lind. This is a moot point, since Dr. Dawes, of Oxford, has said that in the newborn lamb there is no murmur heard if the ductus is either widely open or tightly closed. If the ductus is only a little bit open, the constriction is felt to produce the murmur.

We have been told by our cardiologist that any child who has an opening of whatever size at a later age should have a murmur.

It looks as though Dr. Adams and Dr. Lind may have established the fact that the ductus may be open in the human newborn infant—as in the newborn lamb—and no murmur be heard. If this is so, it makes considerable difference in judging our newborn infants clinically.

DR. ROBERT KAYE, Philadelphia: I'd like to ask Dr. Rowe a question.

I find it difficult to understand the functional significance of a rise in pulmonary pressure above systemic pressure with anoxia. Increase in pulmonary pressure might limit the left to right shunt favoring the blood supply to the brain, but a rise above systemic pressure would decrease the oxygen saturation of the cerebral circulation by shunting unoxygenated blood into it.

DR. JAMES DRORBAUGH, Boston: I'd like to ask Dr. Adams a question.

If I understood correctly, his experiments establish that there's high pulmonary artery pressure in the full-term newborn infant. Most of our infants with respiratory pulmonary difficulty at birth are in the smaller weight groups. I'd like to ask him what the findings might be in slightly premature humans or animals?

DR. NELSON K. ORDWAY, Chapel Hill, N. C.: Would Dr. Adams comment on the arterial-venous oxygen differences observed in these children? I tried to infer them from the slide, and it looked as though they might be quite wide.

I'm interested if he would comment further on the relation between pulmonary and systemic blood flows. It looked to me as though two of his infants had pulmonary flows between 6 and 10 times the systemic flow. About five or six times the systemic flow is about as much as we ever see at catheterization of children and older persons with left-to-right shunts, and such patients are in moderately serious condition. If Dr. Adams' figures are right, they presumably would imply a rather temporary duration of the marked left-to-right shunt.

Would Dr. Rowe comment on the low arterial oxygen saturation observed in the infants who were breathing 100% oxygen? The administration of 100% oxygen to a child with heart disease has been a useful tool in enabling one to rule out the presence of a right-to-left shunt. If his figures were all less than 100%, does this imply that these children might have had right-to-left shunts, or is the low saturation an artifact?

DR. SAMUEL Z. LEVINE, New York: May I ask whether the insertion of a catheter into a relatively constricted patent ductus might not alter the natural pressure relationships between the right and left sides of the heart?

DR. BENJAMIN KRAMER, Brooklyn: I believe many of you are familiar with the work of Dr. Reynolds, in which he studied animals before and immediately after birth and found a minimal circulation through the lungs. With birth apparently new beds of capillaries seem to open up. Pulmonary circulation increases tremendously, and pulmonary arterial pressure drops.

PRESIDENT ZUELZER: The Chairman was worried earlier that perhaps the discussion might be too tame and that there might be too much agreement, but I think we have passed that danger.

DR. FORREST H. ADAMS, Los Angeles: I want to thank everyone for their stimulating discussion.

Dr. Smith, the reason for the absence of the murmur was the first question that others have asked. In this regard I'm sorry Dr. Dawes isn't here to give his concept in the lamb. He has shown, in the lamb, that the presence or absence of the murmur is related to the degree of turbulence. Since we have made no calculations regarding the Reynolds number in these human infants, I can say nothing about the degree of turbulence present; but no murmurs were heard on auscultation by either Dr. Lind or myself.

Dr. Ordway was correct in assuming that the arterial-venous oxygen difference was quite large in some instances. Dr. Joan Mott, of the Nuffield

Institute, and some others have pointed out that perhaps in some instances the tip of the catheter was at the orifice of the ductus arteriosus, and so we were getting the stream of head aortic blood on right into the tip of the catheter. In order to be accurate in our pulmonary blood flows, we should have obtained samples from the left and right pulmonary arteries and averaged them. This, we didn't do, but it should be done.

Dr. Levine asked if the catheter was in the ductus arteriosus might the pressure relationships be altered?

Well, actually, we never took pressure recordings in the ductus arteriosus but from experience with larger infants the answer would be no.

DR. RICHARD D. ROWE, Toronto: I'm afraid I have no good answer to the question of what the purpose of the reversal of flow, or return to the fetal situation, is in the younger infant group which was subjected to hypoxia.

As far as Dr. Ordway's question goes, the question of the low level of arterial oxygen saturation with the 100% oxygen administration may be related to the method we used, and on reviewing other normal infant catheterization studies that have accumulated over a five-year period I find that there are a number of these in which similar results were obtained, so that possibly it's a method artifact.

Measurement of Pulmonary Flow and Intracardiac Shunts by Respiratory Gas Analysis: Modernization of a Douglas-Haldane Technique. JOHN J. OSBORN, Stanford.

A cardiac catheterization, especially in a child, is almost a major operation. Its repeated use is limited by its expense and complexity. Its information although very accurate is essentially limited in children to the resting, anesthetized state. We would often like to make repeated observations of cardiac output or percentage of intracardiac shunting, or to compare observations at rest with those during exercise, but this is very difficult by catheterization techniques.

We have developed a method of estimating pulmonary blood flow and left-right shunting based on analysis of respiratory gas for CO_2. This is an extensive modification of the old Douglas-Haldane technique using modern rapid instruments. Samples of alveolar air (essentially equilibrated with pulmonary venous blood) and of air equilibrated with pulmonary arterial blood are obtained by a semi-automatic technique, and immediately analyzed for pCO_2 and recorded by an infra-red CO_2 analyzer. At the same time, total expired CO_2 is measured.

From these data the pulmonary flow can be calculated by the modified Ficke Principle. Also, considerable information can be gained from variations in pulmonary arteriovenous difference in pCO_2 under different conditions of rest or exercise. For instance, changes in quantity of left-to-right shunting can be demonstrated. Simultaneous ear-oximetry may detect changes in right-to-left shunts.

Measurements may be completed within two minutes or less, and may be repeated as often as necessary. Because the procedure is not painful or frightening it is applicable to the unanesthetized child. Cooperation of the patient is not required; hence, measurements can be made on very young children.

The technique will be described, and examples will be shown of information gained which could not be obtained by routine catheterization.

Intracardiac and Peripheral Plasma Oxygen Tension Levels, Diagnostic and Therapeutic Investigation. BRUCE D. GRAHAM, MURIEL H. BAGSHAW,* AARON STERN,* JAMES L. WILSON, WITH ASSISTANCE OF M. U. TSAO,* and CHARLES SLOAN,* Michigan.

It has long been assumed that oxygen administered to a patient with congenital heart disease with a right to left shunt would not improve the systemic arterial hemoglobin saturation unless there was associated mechanical heart failure with pulmonary edema. This assumption has been based upon the following facts: first, that blood bypassing the lungs through a right to left shunt is not influenced by alveolar oxygen, and, second, that from the nature of the oxygen dissociation curve the nearly saturated hemoglobin cannot take up significant additional oxygen. Finally, plasma oxygen has been assumed to be quantitatively unimportant. A polarographic method modified in this laboratory for the determination of plasma oxygen has been applied to this problem.

In spite of this theory it is the impression of some that certain patients with cyanotic heart disease do appear less cyanotic with administration of high concentrations of oxygen. Therefore, a number of children with cyanotic congenital heart disease due to shunts were studied during cardiac catheterization. Intracardiac and peripheral systemic blood samples were obtained while these patients were breathing room air and higher concentrations of oxygen. Results for blood pH, CO_2 content, (calculated pCO_2), hemoglobin saturation, and plasma oxygen tension were obtained. A definite increase in both hemoglobin saturation and plasma oxygen tension levels in both the systemic and pulmonary circuit was demonstrated. The role of extrapulmonary hemoglobin saturation in these patients will be discussed with reference to the effectiveness of plasma oxygen in oxygen therapy.

The use of plasma oxygen tension levels as an ancillary tool of investigation during cardiac catheterization will be discussed. For example, the enormity of the physiologic handicap resulting from an interauricular shunt is demonstrated by a tre-

mendous change in the plasma oxygen tension levels in the right auricle when the patient breathes known high oxygen concentrations instead of room air. Slight changes in hemoglobin saturation did not reveal this physiologic fact.

Other data obtained from different children with congenital cardiac disease indicate that the ease of oxygen transfer across the pulmonary membrane often will be apparent from pO_2 changes but will not be revealed by the usual hemoglobin saturation. This will be illustrated with specific examples.

It is further demonstrated that the benefit derived from oxygen therapy is more apparent from plasma oxygen tension (pO_2) levels than from determinations of hemoglobin saturation in the presence of pumonary changes secondary to large left-to-right ventricular shunts. These results indicate that oxygen therapy is often of benefit despite some decreased pulmonary efficiency.

DISCUSSION

DR. JOSEPH DANCIS, New York: I'd like to ask Dr. Graham if he has had an opportunity to measure the effects of prolonged high oxygen administration—100% oxygen administration—to some of his patients. There is evidence of adverse effects on the lungs if the administration is prolonged over too great a period of time.

The question is a practical one. Should we consider the use of 100% oxygen as a therapeutic agent over a long period of time?

DR. JAMES MANNING, Rochester, N. Y.: Do you know what happened to the total pulmonary blood flow during this period of high oxygen concentration breathing?

DR. NELSON K. ORDWAY, Chapel Hill, N. C.: I hope that Dr. Osborn is on the track of something really precise that can be exploited to a great extent in the study of patients with congenital heart diseases. We have had need for some years of an accurate method for measuring pulmonary flow.

The principle of this technique was applied some years ago by Bing, Vandam, and Gray, using carbon dioxide inhalation, in an attempt to measure the degree of extracardiac left-to-right collateral in patients with cyanotic heart disease. The analysis of their data and their technique, which is no longer used, would indicate that the errors are so great that there is very little application of this to small changes in pulmonary flow.

It is possible in the presence of a right-to-left shunt of some magnitude to indicate very precisely what the possible limits are of pulmonary flow, if one knows the systemic blood flow. I wonder whether use of this simple mathematical technique might not be of value to Dr. Osborn in checking his observed data with those which he can calculate from patients with moderately large right-to-left shunts, if he knows their systemic flow.

The beauty of his method, if it is going to work out, is that it enables one to determine arterial gas content at the precapillary level. It therefore might, perhaps, afford an answer to some of the objections or speculations that were raised in connection with the paper by Dr. Adams, who pointed out the difficulty that one has in being sure that one has a truly representative sample of mixed blood distal to the shunt in cases of patent ductus arteriosus.

I'm not quite sure I understand what Dr. Graham means by extrapulmonary addition of oxygen. As he points out, this is oxygen in solution. This is then transferred to the reduced hemoglobin of the shunted blood because of the equilibrium between oxyhemoglobin and oxygen tension, once the superoxygenated blood has passed beyond the lungs and mixed with the shunted blood.

Actually, I might point out that the maximum increase in arterial oxygen saturation that one can achieve by giving oxygen is of the order of 10%, a theoretically predictable figure, when you realize that by giving 100% oxygen one achieves an increment of about 2 vol.% of dissolved oxygen; 2 divided by the usual normal oxygen capacity of 20 vol.% is 10%, expressed in terms of oxygen saturation. The child or children shown by Dr. Graham with an increment in oxygen saturation of less than 10% on oxygen inhalation were either breathing oxygen at less than 100% saturation or were countering its effect by increasing the volume of a right-to-left shunt, perhaps due to struggling incident to the application of the mask.

DR. JOHN J. OSBORN, San Francisco: In answer to Dr. Ordway, we are in the process now of trying to evaluate how big the errors are in this technique, and the only way to really do that is to study many children both by this technique and by catheterization. Incidently, we badly need a system for systemic flow that is anywhere nearly as good as we believe this is for pulmonary flow, because we are stuck when we try to actually measure how much blood is shunting. We can't measure the systemic flow, so we have no basis to calculate the shunt accurately.

I didn't quite understand all of what Dr. Ordway said. I believe I'll have to look him up after the meeting.

This system that we have been working on, incidentally, is not as much help in evaluating right-to-left shunts. It is much more useful in left-to-right shunts.

DR. BRUCE D. GRAHAM: First, in reply to Dr. Dancis' question as to the effect of prolonged oxygen administration, we purposely stayed within the realm of usual oxygen therapy concentrations. We carried them on these amounts not very long

at a time, nor would I expect a deleterious effect on lung tissue with these concentrations of 40% and 60%.

In response to Dr. Ordway, I'm afraid it's just a question of semantics in trying to use a catchy phrase. We did not mean to imply at all that we had here anything except the fact that the plasma carried the oxygen down below the shunt, and there, as you say, it contributed oxygen to the unsaturated hemoglobin.

One point that Dr. Ordway makes I can go along with halfway, and that is that you can contribute using 100% oxygen up to something like 2 vol.% additional oxygen.

Now, as Dr. Conroe calculates, when we add this oxygen to the arterial-venous difference or above and beyond the arterial-venous difference, which is usually about 5 vol.%—that is, the usable oxygen—then you can see percentagewise what you are offering is considerably more. We use that rationale with these patients.

Venous and Arterial Pressures in the Normal Newborn Infant. P. M. TAYLOR,* T. J. EGAN,* and F. J. MCARDLE,* Pittsburgh. (Introduced by Robert Klein)

Determinations of venous pressure have been obtained from birth to 2 days of age on normal infants, both term and premature. A polyethylene catheter is advanced through the umbilical vein and ductus venosus, so that the tip of the catheter rests near the junction of the ductus venosus and inferior vena cava. Initial readings are made prior to clamping the umbilical cord and in some instances before the onset of respiration. Measurements of arterial pressure (systolic, diastolic, and pulse pressure) have been recorded, in some cases, simultaneously with the venous pressure readings from a catheter in an umbilical artery. The catheters are left in place until the pressure readings stabilize. Venous pressures have been repeated thereafter at frequent intervals on several infants.

The influence of the onset of respiration, clamping the cord, and cessation of pulsation of the unclamped cord on arterial and venous pressures will be discussed. Venous pressure at birth ranges from 150 to 200 mm. of saline, dropping, over the first hour or two of life, to from 50 to 100 mm. of saline, at which level it is maintained thereafter. Possible explanation of this finding will be discussed.

It is planned to obtain similar observations on infants with neonatal respiratory distress, as it is conceivable that abnormal alterations in the circulatory dynamics of the newborn infant might play a role in the pathogenesis of the pulmonary hyaline membrane syndrome. It is also possible that, once established, severe neonatal respiratory distress (atelectasis with pulmonary hyaline membrane) might give rise to acute right-sided heart failure. This possibility is supported by clinical observations.

DISCUSSION

DR. HERBERT C. MILLER, Kansas City, Kan.: In this paper and in several of the papers that were presented this morning, the term "normal newborn" was referred to but not critically defined. I suppose the studies that we have just seen are an attempt to define in more critical terms the normal newborn infant, but I would have some doubts as to whether or not all of the 10 cases presented here could be described as "normal" if submitted to a really critical examination.

I say that because in our experience a normal newborn, at least from the respiratory point of view, is one that breathes at an average rate of about 40 respirations per minute with a standard deviation of plus or minus 8 beginning the first hour, and continues to breathe at this rate for the next several days under sleeping conditions. All babies that do not respire in the above manner tend to show deviations in pCO_2, pH and O_2 saturation of their blood. Some of the 10 infants just presented had respiratory rates that would put them in the abnormal group according to our standards. Because of the close relationship between respiration and circulation, it seems to me a bigger effort must be made by those studying cardiac conditions in the newborn to define in more critical fashion what is meant by the term "normal newborn infant."

DR. STUART S. STEVENSON, Pittsburgh: I know how carefully these babies were picked; this was obviously a hazardous procedure. Dr. Taylor tried extremely hard to get babies who, by any reasonably critical standards, promised to be normal. You will recall there was one death, but I believe it would be very much of a coincidence if he picked 10 babies, all of whom were abnormal.

DR. P. M. TAYLOR: In answer to Dr. Miller, I don't believe we could say definitely that the babies were all normal. We did, as Dr. Stevenson indicated, attempt to take every reasonable method of finding out, though, that they were as normal as possible.

We abandoned doing venous pressure studies on any infant who did not seem to be in good shape at delivery. We have followed respiratory rates every four hours on these infants for 24 hours—sometimes longer—and we have followed pulse rates on not all the babies, but on most of them.

In one infant, as you noted from one of the slides, there was an increase in respiratory rate to greater than 40, the figure which Dr. Miller feels to be normal for infants. This infant's respiratory rate came down rapidly, he was not dyspneic at any time, and we felt he was in good shape once he recovered from this short period of anoxia.

Studies of Carbohydrate Metabolism in the Newborn. MARVIN CORNBLATH,* EPHRAIM Y. LEVIN,* and ESTELA MARQUETTI,* Johns Hopkins. (Introduced by Harry Gordon)

In order to elucidate some aspects of carbohydrate metabolism in the newborn, capillary blood sugars as well as capillary-venous (c-v) differences have been determined. The subjects studied were normal full-term infants in the fasting state and after the administration of oral glucose, intramuscular epinephrine, and intramuscular or intravenous glucagon.

Capillary-venous differences may be used as a guide to peripheral utilization in the limb studied and may be influenced by some hormones. Because these differences are often small, the precision and reproducibility of the glucose analyses were determined in 69 pairs of separately pipetted blood samples. Twice the standard error of the difference between such determinations was found to be 3.2 mg. per 100 cc. in our laboratory. C-V differences of 4.0 mg. per 100 cc. or greater were accepted for interpretation.

Capillary-venous differences were determined 67 times in 55 unfed infants. There was a rough inverse correlation with age and a direct correlation with capillary sugar level. The latter was shown more clearly in 11 infants following the administration of glucose, which produced both a rise in capillary glucose and an increase in c-v difference. In 11 infants studied after use of epinephrine, this rise in capillary glucose was usually accompanied by either no increase or a diminution in the c-v differences. Except for the delay in peak capillary sugar following epinephrine (Desmond, Hild, and Gast, 1950), the response of the fasting normal neonate to both glucose and epinephrine was similar to that of the adult.

The administration of glucagon I. M. or I. V. to 17 infants on the first day of life produced a prolonged rise in capillary sugar. As the infants became older, the period of hyperglycemia was shorter, the curve resembling the curves obtained in older children and adults. The c-v differences showed only slight increases, suggesting a minimal increase in peripheral utilization.

Studies are continuing of the offspring of diabetic mothers and of premature infants.

DISCUSSION

DR. JOHN A. ANDERSON, Minneapolis: I have two questions I'd like to raise in the light of what was presented in the cardiophysiologic papers this morning concerning the possibility of a transitory reverse ductus flow occurring in the immediate newborn period. I believe this was also demonstrated by Eldridge in the July, 1955, *Journal of Clinical Investigation* by capillary-blood-oxygen studies in the heel and in the finger blood of newborn babies.

One then wonders if you can be certain that you are having a true arterial sample, particularly in the foot, if there is a possibility that pulmonary blood has been shunted out into the arterial system for the moment. This would, of course, produce variation in A-V differences of glucose as well and the interpretation of the results might be influenced because of that possibility.

Another point is this: In some observations of a similar nature we have felt it is certainly more advisable to do the venipuncture in the limb first and then wait until the baby has stopped crying and has recovered from this before one does a superficial cut in the heel to obtain the capillary blood that may be there after the time of sticking. This seems to present a little greater A-V difference under such procedure.

DR. ROBERT ULSTROM, Los Angeles: We have studied the fasting blood of the newborn infant on the first day of life, using the same chemical method, and have found from approximately 10% to 40% of the reducing substance measured by this method can be nonfermentable. In general, a correlation existed with the total height of the sugar—in other words, the height of the nonfermentable reducing substance correlated quite well with the height of the total reducing substance mentioned.

More recently, we have found, with some consistency, a substance that appears to be fructose on paper chromatograms in the cord blood.

Since fructose is a fermentable sugar, the discrepancy between fermentable and nonfermentable reducing substances found is not explained. No other reducing but nonfermentable substances were found on the cord-blood chromatograms.

DR. ANDREW SASS-KORTSAK, Toronto: Dr. Cornblath has shown that negative arteriovenous differences may be observed. I wonder whether he could give his views explaining this rather unusual phenomenon.

DR. FREDERICK W. BARNES JR., Baltimore: Dr. Andrews and Dr. Zierler have shown in the adult that the A-V differences for muscles are so small as to account for only a very small fraction of the total metabolism of the muscle, and, at present, they are working on the possibility of fatty acid being a much greater source of muscle energy than had been previously thought.

I wonder what you thought about the fatty acid in this connection, and perhaps, more particularly, whether you feel that your data suggest that in the newborn glucose is not quite an adequate source of the major energy requirements.

DR. SAMUEL P. BESSMAN, Baltimore: I'd like to ask Dr. Cornblath if he has available the data on the fasting blood sugar levels of the prema-

tures who showed such a small response with glucagon. Perhaps he might be able to get a suggestion from this as to the mechanism of hypoglycemia in newborn infants. If there is no response to endogenous glucagon, this may be an explanation.

DR. MARVIN CORNBLATH: I want to thank all the discussers.

In answer to Dr. Anderson's comments about back flow in arterial blood samples in the newborn, we deliberately reported our results as capillary-venous differences, rather than arterial-venous differences. In fact, we found that the arterial and capillary sugar levels were significantly different in 7 of 16 instances and therefore the data represent capillary-venous differences.

We have not done venipunctures first. The main objection to doing venipunctures first is that spasm of the artery can occur with resultant diminished flow to the extremity.

Dr. Ulstrom's comments are very provocative. I believe the finding of significant amounts of fructose in the blood in the newborn is new and extremely interesting. Dr. Villee, of Boston, had investigated this problem previously and found only very small concentrations of fructose (2-3 mg. per 100 cc.) in newborn blood.

I don't know if he used barium and zinc as the precipitating agents in analyzing for true sugar. I believe the precipitation step is the important one in getting rid of non-sugar-reducing substances.

In explaining the negative c-v differences, I believe there are at least two possibilities. One is that the negative c-v differences might be due to technical difficulties. We do not obtain the blood samples simultaneously and some evidence has been reported that the blood sugar may change rapidly.

The other possibility is that the negative c-v differences reflect a true increase in sugar in the vein, as compared with that in the capillaries. There are several mechanisms possible. It has been shown by Park and co-workers at Vanderbilt that free glucose can diffuse into the muscle cell and it is possible that back-diffusion could occur. In addition, as muscle glycogen is utilized and as each branch point is split, there is a mole of free glucose liberated by the action of amylo-1-6-glucosidase. Actually about 12% of glycogen utilized can appear as free glucose. A third possibility is that the increased reducing substance in the venous blood is a substance other than sugar.

Negative c-v differences are not unusual at these blood sugar levels and have been reported in adults and children.

Our data cannot be used for balance work, since we have many uncontrolled variables, the most notable being blood flow. Drs. Zeiler, Cader, and Andres have been doing careful balance studies sampling blood from the antecubital artery and vein, with the hand excluded. Their results are applicable to balance analysis.

In answer to Dr. Bessman's question, the mean fasting sugar levels in the younger premature infants was 43 mg. per 100 cc., compared with 48 mg. per 100 cc. for the full-term infants. In the older groups, after various fasting periods, the mean blood sugar for the older prematures was 54 mg. per 100 cc. and for the older full-term infants, 59 mg. per 100 cc.; so I don't believe these differences can account for the response.

Blood Pyruvic Acid Levels in the Newborn Infant: Demonstration of a Concentration Gradient Between Maternal and Cord Circulation. ROMULO F. GONZALES* and LYTT I. GARDNER, State University of New York, Syracuse.

Determinations of blood pyruvic acid concentration have been made in full-term newborn infants from the time of birth to the fifth day of life. Similar data were obtained from normal, nonpregnant adults and women during pregnancy and parturition. Measurements of pyruvic acid concentration were made on simultaneously collected venous and arterial umbilical cord blood specimens obtained from normal vaginal deliveries.

The maternal blood pyruvic acid concentration during pregnancy and parturition was not significantly different ($P>0.1$) from the values obtained in adult controls (mean$=1.09\pm0.36$ mg/100 ml.).* The pyruvic acid level during the third stage of level was not elevated over values obtained during the first two stages of labor. The mean umbilical cord arterial blood level of pyruvic acid (1.48 ± 0.43 mg/100 ml.) was significantly higher ($P<0.01$) than the mean cord venous blood level (1.25 ± 0.38 mg/100 ml.). The mean umbilical cord arterial blood level was significantly higher ($P=0.01$) than the mean level in maternal blood during childbirth (1.18 ± 0.44 mg/100 ml.). In the full-term newborn infants the mean blood pyruvic acid level was found to fall step-wise from the first to the fourth 24 hours of life, when it equaled the mean adult normal value.

The data suggest that the "elevated" concentration of blood pyruvic acid in the newborn infant during the early postnatal period is a product of fetal rather than maternal metabolic processes. It is postulated that this is due to the preponderance of the anaerobic over the aerobic type of metabolism in the infant during the fetal and immediate postnatal period. This may mean an increased production and/or diminished utilization of pyruvic acid by the fetus and the newborn infant.

* $\pm$=Standard Deviation.

DISCUSSION

DR. ANDREW SASS-KORTSAK, Toronto: About four or five years ago we measured pyruvic acid levels in infants suffering from various toxic diseases. We found—and I believe others since then have found the same thing—that pyruvic acid levels are elevated in these states.

I was just wondering whether the shock of delivery may have something to do with the elevation of blood pyruvate that Dr. Gonzales has observed, although the rather slow return of the pyruvic acid levels to normal would rather be against this suggestion.

DR. ROMULO F. GONZALES: We were aware of the factors that were involved pathologically, so in this study we made sure that these babies were normal newborn infants.

We also tried to eliminate any babies that showed any prenatal abnormality, including any abnormality in delivery.

The in Vitro Metabolism of Tyrosine and Its Intermediates in the Liver of the Premature Infant. NORMAN KRETCHMER, S. Z. LEVINE, and HELEN MCNAMARA,* Cornell.

Tyrosyluria was first described in the premature infant in 1939 and was shown to result from a lack of supplementary vitamin C in the diet. Since then, the in vitro metabolism of tyrosine has been intensively studied. It was shown, by many authors, that the oxidation of the *p*-hydroxyphenylpyruvate resulting from the transamination of tyrosine required vitamin C. If the appropriate enzyme and vitamin C were present, the *p*-hydroxyphenylpyruvate could be oxidized to homogentisate. Further oxidation of this latter compound ultimately resulted in acetoacetate.

Work done in this laboratory showed that there was a lack of tyrosine oxidizing activity in the liver of the premature infant. This finding could be explained in part by lack of tyrosine transaminase activity or concentration.

The present study indicates that there is also a lack of *p*-hydroxyphenylpyruvate oxidase activity. Partial activity of this enzyme could be obtained when large quantities of ascorbic acid were added in vitro (10 to 15 mg. versus the usual 0.5 mg.). It also would appear that the response of the enzyme to ascorbic acid may be dependent upon the weight of the infant. The clinical manifestations of tyrosyluria will be discussed relative to these in vitro findings.

DISCUSSION

DR. DAVID YI-YUNG HSIA, Boston: I should like to ask Dr. Kretchmer if he has been able to carry this reaction in tissue, in ascertaining the enzyme in the absence of ascorbic acid, especially in the presence of dichlorophenolindophenol (DCPP), which has been discovered to be an adequate substitute.

DR. ROBERT A. ALDRICH, Portland, Ore.: Here we have an enzyme system which has many of the characteristics of 11-betahydroxylase found in the adrenal cortex, a place where there is plenty of ascorbic acid.

In our laboratory, using oxygen^{18}, we have shown that free oxygen is the substrate for this hydroxylation. This and other considerations make it appear that some peroxidase-like enzyme (possibly catalase) is functioning.

If this is true, it would be the first example of catalase acting in an oxidation system using a biological substrate.

DR. SAMUEL P. BESSMAN, Baltimore: About two years ago, Udenfriend showed that if you take ferric ion, tyrosine, and ascorbic acid, you can hydroxylate aromatic compounds in a manner exactly mimicking the normal manner of oxidation in the animal, whereas the chemical reactions for hydroxylation are different.

Now, there's a question I'd like to ask. If you add so much ascorbic acid, if you require so much ascorbic acid to perform the oxidation in the premature liver, which has a deficiency of iron, could one be dealing with a nonenzymatic process here and pushing it with the enormous amount of ascorbic acid that you use?

DR. NORMAN KRETCHMER: In answer to Dr. Hsia, we have tried this reaction in the absence of ascorbic acid. The reaction goes at about 20% of the maximum rate when either the liver of the adult human or rat is used. This reaction does not occur at all with the liver of the premature infant.

Dichlorophenolindophenol, or DCPP, does not activate the immature infant liver but does activate the adult liver.

I should like to thank Dr. Aldrich for his comments, and I was aware of his O^{18} material. It is surprising that molecular oxygen participates in the formation of the hydroxyl group of the steroid. We have been rather interested in the hydroxylation of *p*-hydroxyphenylpyruvate which results in homogentisate. The data presented by Dr. La Du in *Nature* and at the recent biochemical meetings in Atlantic City brought up a point which I believe demands a good deal of discussion. Dr. Britton Chance discussed the function of catalase in the hydroxylation, which, as Dr. Aldrich said, would be the first example of catalase catalyzing a hydroxylation reaction. Actually, La Du's catalase was 86% pure and there was no knowledge of the other 14%. I believe it would be more likely that this was a peroxidase catalyzed reaction.

Finally, Dr. Bessman mentioned Dr. Udenfriend's in vitro nonenzymatic system using ascorbic acid and a hydroxylation substrate. The question of the nonenzymatic hydroxylation occurring in immature infants can be partially answered by experiments where iron has not been necessary for the conversion of *p*-hydroxyphenylpyruvate to homogentisate.

Blood Ammonia in Various Conditions and Its Contribution to Mental Symptoms. SAMUEL P. BESSMAN, Maryland.

The blood concentration of ammonia in various pediatric conditions will be discussed in the light of the role of ammonia in the production of mental confusion and coma in adults. Elevated levels of ammonia, equal to the values found in confused states and coma in adults, have been found in some cases of prematurity, postmaturity, and in patients with erythroblastosis fetalis. The effect of exchange transfusion on blood ammonia will be described.

Animal experiments on the renal metabolism of ammonia as affected by the carbonic anhydrous inhibitor, acetazoleamide (Diamox), will be presented, and evidence concerning its site and mechanism of toxicity will be discussed.

The toxicity of parenteral ammonium chloride in the treatment of hypochloremic acidosis will be considered and data on a technique for the relief of this condition by the use of sodium glutamate will be presented. A fall of blood ammonia from 10 gamma/ml. to normal in 90 minutes by the use of glutamate will be described.

The use of asparagine experimentally for the treatment of epilepsy will be discussed in the light of the effect of asparagine on the blood ammonia concentration.

Various nitrogenous agents such as asparagine, glutamate, and arginine cause a marked drop in blood ammonia at proper dosage. Examples will be given.

The role of ammonia in pediatric conditions of impaired consciousness will be discussed.

DISCUSSION

DR. JOHN A. ANDERSON, Minneapolis: I'm extremely grateful to Dr. Bessman for this method. For the last eight months or so, we have been using the micro Conway diffusion technique for the immediate (3-5 in.) ammonium value in the blood in a variety of pediatric conditions, which include several observations in the newborn and also three babies with erythroblastosis.

The observations that we have made so far in these three infants confirm what he has presented. We have followed serially the ammonium values in the newborn period, taking maternal bloods, cord bloods, and then doing three-, four-, five-, or seven-day samples during the course of the physiologic icterus.

In these observations during physiologic icterus—I believe about 9 or 10 at the moment—we have not encountered a rise in the ammonium values equal to those observed in the exchanged erythroblastotic children.

There also appears to be a slower decline in the post-exchanged, transfused child.

It also appears that the administration of ammonium chloride to mothers in the later days of pregnancy produces a low pH in their infants at birth. The ammonium values in the mother's blood may be occasionally elevated above normal. We have, however, not encountered a significant elevation in the cord blood of the babies born from such mothers. The implications that the ammonium ion is a contributing factor to brain injury, as Dr. Bessman has indicated, is, of course, most interesting, and it would require a great deal of investigation to know whether it is of primary or of secondary interest.

DR. RICHARD DAY, Brooklyn: My question refers to a somewhat similar point to one touched on by Dr. Anderson.

Mention was made of ammonia levels in infants who seemed to be tolerating rather extraordinary degrees of jaundice. It would be interesting if these were low. Were they?

DR. GILBERT B. FORBES, Rochester, N. Y.: I wish Dr. Bessman would compare the blood levels of ammonia in erythroblastotic infants with those in persons suffering from true hepatic coma.

In experiments some years ago in both children and animals given ammonium chloride, we failed to note any symptoms of ammonia poisoning when levels were much below 3 gammas per cubic centimeter, and I wondered, therefore, if it was possible to ascribe all the symptoms observed in your subjects to this rather mild elevation in blood ammonia level.

DR. SAMUEL P. BESSMAN: I just want to say one thing in terms of Dr. Anderson's statement about ammonium chloride toxicity, and that is that Dr. Harry Gordon published a paper several years ago which he very kindly gave me, which showed that premature infants, if I remember correctly, were not able to tolerate test doses of ammonium chloride as well as older infants.

This may answer Dr. Forbes' question, also, that these infants couldn't tolerate doses of ammonium chloride, and yet they didn't show any significant difference in pH of the blood. Dr. Gordon suggested that this might be an inability to handle the chloride ion. I wish he were here to say something about it, because he mentioned that it might be due to ammonium-ion toxicity itself.

In relation to Dr. Day, we measured a lot of infants with physiologic jaundice, and they didn't have greatly elevated blood ammonia. I don't venture to say that ammonia is the cause of the symptoms, but it certainly can sensitize the organism or sensitize the brain particularly to the poisoning from bilirubin; furthermore, the question of the ammonium level is not important, it's the time over which a small elevation in ammonia is active.

A high level acutely or a slight increase over a long time can produce the same result in attrition of the Krebs cycle.

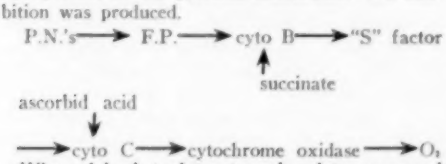
Bilirubin Encephalopathy: Studies Related to the Site of Inhibitory Action of Bilirubin on Brain Metabolism. WILLET R. BOWEN, M.D.,* and WILLIAM J. WATERS, M.D., Syracuse.

This study was undertaken to demonstrate where the site of inhibition in aerobic brain metabolism is produced in bilirubin encephalopathy. The present findings are based on the following oxidation scheme in newborn rat brain homogenates:

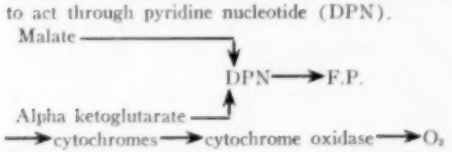
Pyridine nucleotides (DPN, TPN) → flavoproteins → cytochromes → O_2

Previous studies have shown that the pigment within the brain cell in hemolytic disease of the newborn is bilirubin and that it produces a 67% inhibition in O_2 consumption in the newborn rat brain homogenates, in contrast to 22% inhibition in adult rat brain homogenates.

If bilirubin inhibits at the cytochrome C level, then when succinate or ascorbic acid is used as a substrate inhibition should be demonstrated, since both act through the cytochromes and not flavoprotein or the pyridine nucleotides. No inhibition was produced.



When alpha ketoglutarate and malate were used as substrates complete inhibition was demonstrated. Alpha ketoglutarate and malate are known to act through pyridine nucleotide (DPN).



This inhibition was reversed by the addition of oxidized DPN.

Using reduced DPN as a substrate it was found that there was a complete inhibition on a 1:1 molecular basis of DPNH and bilirubin and that this inhibition could be reversed by increasing the concentration of DPNH.

Oxidized DPN or TPN when added to a control flask increased the O_2 consumption one- to twofold but when bilirubin was added this effect was completely blocked.

Day has previously suggested that inhibition in aerobic brain metabolism may take place at the cytochrome level. From the studies presented, it would appear that inhibition takes place at the pyridine nucleotides (DPN and TPN) level and is reversible.

DISCUSSION

DR. RICHARD DAY, Brooklyn: I'm very glad to see somebody with a chemical bent take this work over, especially at Syracuse, where Dr. Gardner works. He was the one who first suggested testing bilirubin in vitro.

I should like to ask Dr. Bowen if he has attempted to test hematin. As you know, a substance similar to hematin has been advanced by some workers as a possible cause of kernicterus. We found that hematin will inhibit brain metabolism. A curious difference between hematin and bilirubin is that hematin will not depress the motility of one-celled animals, but bilirubin will. We found hematin to be inhibitory of oxygen uptake of fresh tissue in the presence of succinate.

DR. SAMUEL P. BESSMAN, Baltimore: I'm interested in this from two standpoints.

The first is that the pH of the medium is very important in determining the reaction of DPN. Particularly, you can break down DPN very easily as soon as the pH gets a little above 7, and I note in the abstract there is a statement concerning an unusual yellow product formed when DPN is reacted with bilirubin.

Now, the bilirubin solution has to be a pretty powerful solution from an ionic standpoint, and also has to be somewhat alkaline, I believe. This yellow product could be the yellow product that is formed by the alkaline deposition of DPN.

The second point is that the succinate system and the ascorbic acid system are both very special in terms of their resistance to chemical injury. They are the easiest systems to maintain. They stay longest, and they are injured by the fewest poisons, whereas the ketoglutarate system is quite a weak system, and so is the malate system.

The question is, is this an osmotic or pH effect, and how did you control your osmotic relations when you added such an enormous quantity of bilirubin?

DR. FREDERICK W. BARNES JR., Baltimore: I'd like to ask Dr. Bowen what he thinks of the possibility of bilirubin acting with DPN in associated systems in other tissues; has he some information on this?

DR. WILLET R. BOWEN: I was very thankful for the comments. Some of them I found rather interesting.

Dr. Day's comment on using hematin in a succinate run—we have concentrated on bilirubin in our studies because by previous work the pigment within the damaged brain cell has been identified as bilirubin and no other hematin pigment was demonstrated.

In answer to Dr. Bessman, I agree that the oxidized DPN was causing the precipitation of bilirubin in the test tube because of a low pH. This is why I left it out of the discussion and made sure the oxidized DPN was buffered up to a pH of 7.6 in the flask runs. In our experience oxidized DPN has not been destroyed when it is buffered up to a pH of 7.6 and was certainly active in our runs. Reduced DPN has a pH of 7 to 7.4. It has been shown that alpha ketoglutarate and succinate are the major pathways in aerobic brain metabolism. (Himwitch and others) In our runs a phosphate buffer and a homogenate are used. The amount of bilirubin added would be insignificant compared with that in the entire system. This would not upset the osmolarity.

To Dr. Barnes I should like to say that was a very interesting question, whether we had tried bilirubin in other tissues to see if it does inhibit. There is conflicting data. I can only tell you what we found.

I tried bilirubin in liver and was not impressed that there was any true inhibition there or tie-up. Other people have reported that they feel there is.

A Difference in Mortality Rate and Incidence of Kernicterus Among Premature Infants Allotted to Two Prophylactic Antibacterial Regimens. WILLIAM A. SILVERMAN, DOROTHY H. ANDERSEN, WILLIAM A. BLANC,* and DOUGLAS N. CROZIER,* Columbia.

Infants under the age of 120 hours who were admitted to the premature nursery of Babies Hospital between December, 1954, and August, 1955, were allocated in random order to one of two antibacterial regimens: (1) oxytetracycline (Terramycin) 5 mg/kg. every 12 hours; (2) penicillin 100,000 units per day and sulfisoxazole diethanolamine (Gantrisin Parenteral) 75 mg/kg. every 12 hours. The conditions of the clinical trial were maintained from admission to the nursery until the age of 120 hours (or death in the interim). Ninety-seven infants were allotted to the oxytetracycline group and ninety-five to the penicillin/sulfisoxazole category.

There was no significant difference between the means of the maximum bilirubin levels achieved by infants in the two antibacterial groups who died.

Twenty-seven infants who were enrolled in the oxytetracycline group died (before the age of 28 days), as contrasted with 60 deaths that occurred in the penicillin/sulfisoxazole category. Although there were no significant differences between the "first day" and "second day" mortality rates in each of the two groups, the "third-day," "fourth-day," and "fifth-day" death rates among infants who received penicillin/sulfisoxazole were substantially higher than those observed among the oxytetracycline controls. A significantly greater number of deaths were observed after administration of penicillin/sulfisoxazole than were noticed following oxytetracycline administration.

A significantly higher proportion of sterile postmortem blood cultures was observed among infants who died in the penicillin/sulfisoxazole group than was noted in infants who received oxytetracycline.

The pathological observations were made with no knowledge of the specific antibacterial regimen which preceded each death. The principal necropsy diagnoses in the two groups of infants who died during the trial period (before age 120 hours) were not significantly different except for the incidence of kernicterus. One example of kernicterus was noted among 16 infants in the oxytetracycline group who died before the age of 120 hours and were examined at autopsy. This incidence was in contrast to 12 instances of kernicterus that were noted among 33 autopsies on infants who died during the trial period and who received penicillin/sulfisoxazole.

The principal necropsy diagnoses among those who died after conclusion of the trial conditions were again not significantly different in the two groups except for the difference in incidence of kernicterus. Nuclear staining was found on seven occasions among 11 autopsies performed on infants who died after penicillin/sulfisoxazole administration. No examples were found in six autopsies performed on infants who died after oxytetracycline administration.

The observed association between penicillin/sulfisoxazole administration prompted a survey of previous experience in the premature nursery of Babies Hospital. For a period of 3½ years penicillin/chloramphenicol or penicillin/oxytetracycline prophylaxis was administered for the first 3 days of life to all premature infants who came to the nursery from outside hospitals (60% of admissions). During this period five examples of kernicterus were observed among 216 autopsies. In contrast to this, penicillin/sulfisoxazole was administered to "extramural" infants for the next 1½ years (immediately preceding the present trial). During this period 29 examples of kernicterus were discovered among 141 autopsies, 27

of these 29 instances occurring among penicillin/sulfisoxazole-treated infants. This evidence lent support to the validity of the observation of the present study that there was a significant association between penicillin/sulfisoxazole treatment and kernicterus.

DISCUSSION

DR. PAUL GYÖRGY, Philadelphia: Several years ago, we proposed a possible working hypothesis on the development of kernicterus. Liver disturbance may play a role.

Today, we heard there were ammonium levels in kernicterus, and that encourages us to bring forward a possible explanation for the observations of Dr. Silverman and his associates. In experimental liver injury we have found that oxytetracycline (Terramycin) and chlortetracycline (Aureomycin) given by mouth will delay development of liver injury, whereas penicillin given by injection—and here I might interpolate that Dr. Silverman didn't say whether the penicillin was given by injection, but I predict it was given by injection—penicillin given by injection or sulfonamide drugs didn't have any effect.

If I understood Dr. Silverman correctly, there was no difference in sepsis.

My humble working hypothesis is that oxytetracycline accumulates in the liver and when given by injection changed the intestinal flora sufficiently so that the liver injury didn't occur.

DR. RICHARD E. FOWLER, New Orleans: Last year, Drs. Elaine Fichter and John Curtis presented before the combined society meetings a paper which discussed the administration of sulfonamides to newborn premature and full-term infants. When we became aware of Dr. Silverman's experiences we called these children back to attempt to determine what had happened to them.

These children were given sulfonamides, which did not include sulfisoxazole—either sulfadiazine or the triple form which included sulfadiazine, sulfamethazine, and sulfapyrazine. We have not been able to do an extensive follow-up on them as yet. Out of a total of 61 children who were in this study at one time or another, we have been able, as yet, to follow up only 33.

Out of this group, we had only two deaths, one a child treated at 30 days of age who died while under therapy. Autopsy findings indicated that death resulted from an acute interstitial pneumonia. The brain was normal.

The other child who died was a premature infant on whom treatment was initiated within the first 24 hours of life, but who died of a Staphylococcus sepsis after five days of therapy. At the time of autopsy, microscopic abscesses were found throughout the body and there was meningitis but no staining of the basal nuclei.

Of this total group of children whom we have been able to follow, only eight actually fit into the same category that Dr. Silverman presented—that is, premature infants treated within the first 12 hours of life. Seven out of these eight prematures are normal, and the eighth is the one that I have just described.

DR. WILLIAM A. SILVERMAN: I have no further comments, except to thank Dr. György for his very interesting suggestion. Actually, the livers have been very carefully examined in retrospect, and these studies may provide a basis for a hypothesis that could be validated only by further investigation. However, in the present report I have presented only the pathologic diagnoses that were established at the time when the examiner had no knowledge of the specific antibiotic regimen which preceded each death. Under these conditions there was no significant difference in the liver lesions noted in the two groups.

Corticosteroid Secretion and Metabolism: Infants vs. Children and Adults. ROBERT S. ELY and EDWIN R. HUGHES,* Utah.

Clinically the impression exists that the infant has a relative inability to meet adequately the stresses which he encounters with acute illness, environmental temperature changes, fluid and electrolyte disturbances, and so forth. It is known that the adrenal cortex plays a fundamental role in maintaining body homeostasis. Therefore, on these clinical grounds plus the results of various laboratory investigations the adequacy of pituitary-adrenal cortical function in the infant has been viewed with suspicion.

Studies of adrenocortical function and of steroid metabolism have been carried out in infants and in older age groups. The subjects studied were normal, with certain disease states also included. The determinations performed include plasma 17-hydroxycorticosteroids (free and conjugated), plasma corticosterone and 17-hydroxycorticosterone, and plasma "total corticoids". Determinations of control samples and samples following corticotropin (ACTH) were made in order to evaluate adrenocortical responsiveness. In several infants, serial corticotropin response studies were performed throughout the first year of life. Also, terminal plasma samples were obtained from several infants, children, and adults so that the adrenal response to agonal stress could be evaluated. The metabolism of several steroids was studied by following their rate of disappearance after intravenous administration. The steroids so studied include cortisol, cortisone, corticosterone, prednisolone, and prednisone.

From these studies there appears to be an age factor influencing adrenocortical function and/or the metabolism of adrenal hormones. The half-life of exogenously administered cortisol is increased with age. Terminal plasma 17-hydroxycorticosteroid values are not as elevated in infants as they are in older children or adults. The pattern, at different ages, of the different steroids determined and the adequacy of adrenal response to corticotropin at these ages will be discussed.

DISCUSSION

DR. ROBERT KLEIN, Pittsburgh: I was very delighted to hear this fine paper by Dr. Ely. It gives me the opportunity to present my paper, which was not accepted—but I won't do so.

We have, I believe, many minor disagreements, possibly due to the question of timing and technique, but there are two points which I cannot, at the moment, compromise with Dr. Ely.

We reported about a year and a half ago that when we gave corticotropin to newborn infants 2 or 3 days of age—and, actually, mostly 2 days—the rise in serum corticoid, using the Nelson method, was even greater, though it was slower than was found in older children and adults, and this was a very marked difference.

The only possible explanation that I have at the moment is that the breakdown was slow. Obviously, this is not true, and I can't understand this.

The other finding that I believe perhaps Dr. Ely might help explain is that the newborn excretion of corticoid occurs in the urine in large part in the free fraction, whereas in the older child and adult it is nearly all bound.

In our using glucuronidase, we have always had some of the corticoid that we could not hydrolyze with glucuronidase, but I believe this may be an error with our method, since we have had some trouble with our glucuronidase products. However, there seems to be more conjugated material unhydrolyzed by glucuronidase that is freed by and in the urine of newborn infants.

DR. MELVIN M. GRUMBACH, New York: I congratulate Drs. Ely and Hughes on their very interesting presentation.

I should like to point out that the levels of corticosteroids found in umbilical cord plasma at delivery do not necessarily indicate production of these substances by the fetal adrenal cortex. In a recent study, performed in collaboration with Migeon and Prystowsky, we demonstrated transfer of free compound F (17-hydroxycorticosterone) across the placenta in the human at term. This passage of hormone from mother to fetus was not by the process of simple diffusion. Whether delivery was by the vaginal route or by Caesarean section and whether compound F or corticotropin was administered to the mother shortly before delivery, the concentration of compound F in the fetal plasma was, in most cases, 20% to 50% of the level in the maternal plasma. Furthermore, in infants delivered by elective Caesarean section, which involves relatively little stress for the mother, compound F in umbilical cord plasma were less than 10μgm/100 ml. and in most instances less than 5μgm/100 ml. These findings indicate that the maternal adrenals, or less likely the placenta, are the primary source of compound F in the umbilical cord blood at term. This also may be true in regard to compound B, although there is no data on this point.

With reference to the values on dying patients, Samuels and his associates have shown that the increased plasma concentration of compound F in these patients does not necessarily mean increased hormone production by the adrenal. Extra-adrenal factors, such as the rate of metabolism and of renal clearance, contribute to the rise in plasma corticoids. In the light of your data, which shows a shorter half-life of administered corticosteroids in infants and young children, may not this more rapid rate of metabolism be responsible for the lower values in dying infants and children as well as the possibility of a diminished response of the adrenal cortex to stress?

DR. LYTT I. GARDNER, Syracuse, N. Y.: In connection with the use of fluorimetric techniques for estimating steroids, we have come across a curious finding recently which I believe is worth reporting. In making extracts of newborn adrenal tissue, we came upon an intensely fluorescent spot in the chromatograms which migrated at about the rate of compound E. The intensity and the unusual characteristics of the natural fluorescence in the ultraviolet of this substance separated it out very easily from compounds E, F, and B, and eventually we came to observe that the fluorescence of this material was identical qualitatively with that of the synthetic vitamin K preparation given every patient on our obstetrical floor. We have found the Rf of this fluorescent substance to be much greater than the Rf of the water-soluble preparation given our parturient mothers (10 mg. of menadiol tetrasodium diphosphate), and much less than the Rf of the fat-soluble menadione. We suspect that we are dealing with an intermediary metabolite of the water-soluble synthetic vitamin K preparation.

CHAIRMAN TALBOT: I should like to ask Dr. Ely to close the discussion, and I'd like to ask him one question myself, namely, whether the test dosages employed in these studies were calculated on a per kilogram or whether they were calculated on a square meter basis.

DR. ROBERT S. ELY: I can answer Dr. Talbot's question first. The dose was on a kilogram basis.

Dr. Klein had two questions. One was in regard to corticotropin in the infant at about the second day of life and the magnitude of response of steroid level.

In our modification of Sweat's fluorometric method we get a magnitude of steroid response which is less than that obtained by the Porter-Silber technique, and that's one reason that we don't get the response that he has shown.

Another thing that I didn't mention is that there is some suggestion in the early life period that we are dealing with a material in addition to Compound F, a material of a fluorescent nature which might represent—although we haven't gone into the matter yet—20-hydroxyhydrocortisone.

The second question of Dr. Klein, regarding the corticoid being largely in the free fraction—I can't answer this question. We have done no studies on the urine of the newborn and early-age children.

Dr. Grumbach's question about transfer across the placental membrane in early life—that is, the influence of maternal corticosterone levels on the corticosterone levels of the young infant—is a very good question. I don't have the answer, since our studies with maternal blood are incomplete at this point. His question, about elevation of steroid levels in terminal cases being the result of delayed degradation, is a perfectly valid question. I don't know quite how we would be able to study this in the terminal patient. At least, we haven't done such studies. I don't believe this would explain the lower terminal values in young infants on the basis of the increased half-life which the young infant shows, because this half-life doesn't seem to be accelerated enough in that early period.

Dr. Gardner's question about the fluorescent materials, I believe, is very interesting. We have done no checking on vitamin K.

The Disturbance of Corticosteroid Synthesis in the Hypertensive Form of Congenital Adrenal Hyperplasia. WALTER R. EBERLEIN and ALFRED M. BONGIOVANNI, Pennsylvania.

Previous studies have demonstrated defective adrenal synthesis of hydrocortisone in congenital adrenal hyperplasia, due to "21-hydroxylase" deficiency, and excessive excretion of pregnane-3γ, 17γ, 20γ-triol in the urine. A study of adrenocortical steroids in the blood and urine of a patient with the hypertensive form of this disease yielded very different results. High levels of Substance S and its metabolite tetrahydro-S were detected in the blood by paper chromatography. From a pool of urine, investigated by means of column and paper chromatography, tetrahydro-S was isolated in large quantity, along with a second steroid not previously described, pregnane-3γ, 17γ, 20, 21-tetrol. The excretion of these substances far exceeded the excretion of pregnanetriol. Pregnane-3γ, 21-diol-20-one, the metabolite of desoxycorticosterone, was isolated from the urine in smaller amount. The excretion of the 17-ketosteroid etiocholanolone was markedly elevated. Study failed to demonstrate any of the normal 11-oxygenated adrenocortical steroids or steroid metabolites in the blood or urine of this patient.

The study demonstrates for the first time an essentially isolated and complete deficiency of "11β-hydroxylase" to be the cause of the hypertensive form of congenital adrenal hyperplasia. Because of this metabolic block the adrenal cortex cannot synthesize hydrocortisone but does manufacture Substance S in large amount. Due to the same deficiency the adrenal secretes desoxycorticosterone instead of corticosterone. The secretion of desoxycorticosterone in turn apparently produces systemic hypertension. Administration of hydrocortisone to this patient caused the blood pressure to return to normal levels at the same time that the abnormal steroids disappeared from the urine.

An investigation of adrenal secretion of desoxycorticosterone, measured by the excretion of its metabolite pregnane-3γ, 21-diol-20-one, in other hypertensive states is reported.

DISCUSSION

DR. ROBERT ULSTROM, Los Angeles: Dr. Eberlein and Dr. Bongiovanni are to be congratulated on further elucidating the possibilities involved in this series of steroid reactions.

We have at this time a patient under study that presents a similar situation to the individual patient mentioned in the paper. This is a very young female pseudohermaphrodite who has no pregnanetriol in the urine, and in whom we have been able to find, by paper chromatography, a compound which is compatible with Compound S.

Feeding this child 17-hydroxyprogesterone failed to cause pregnanetriol excretion in this child.

The child is now about 3 months old and has had no hypertension.

DR. ROBERT ALDRICH, Portland, Ore.: Because of the fact that this particular type of hydroxylation probably involves a peroxidase-like enzyme—or even, conceivably, catalase—one should look into the peroxidase of the leucocytes of this child. If this is a genetic defect, the peroxidase in leucocytes might also be absent.

DR. WALTER R. EBERLEIN: Regarding the comments of Dr. Ulstrom, we'd be happy to study the urine of this patient if you would be willing to send it.

As for Dr. Aldrich, we appreciate your stimulating suggestions, and we'd like to talk to you more at length about them.

Nitrogen Requirements of the Growing Child. SELMA E. SNYDERMAN, L. EMMETT HOLT JR., and PATRICIA M. NORTON,* New York University.

A knowledge of minimal nutritional requirements is important in two general situations: (1) where there is limitation of the food supply and (2) in pathological states which place limitations on the quantity of a nutrient that can be given. Protein requirements will vary with the biological value of the protein or protein mixture fed, a value which is dependent upon the amino acid composition. In establishing protein requirements for various diets, two international agencies (F. A. O. and W. H. O.) have adopted cow's milk protein as a standard of reference. Within certain limits the protein requirement on a specific diet can be related to the requirements of cow's milk protein by a fixed ratio: an increased amount of an inferior protein or protein mixture will meet requirements. However, when the amino acid pattern deviates too far from the optimal this is not possible; no amount of the poor diet will then suffice and supplementation becomes necessary.

Very limited information is now available as to the minimal requirement of the reference protein—cow's milk—at various ages and even less as to the ratios between the reference protein and particular dietary mixtures. The present experiments were undertaken to evaluate the minimal protein requirements of small infants for cow's milk protein. Two infants fed on cow's milk were gradually reduced in protein intake by decreasing the quantity of milk ingested, the calories being made up with fat and carbohydrate. When the protein intake fell below 6% of the total calories (1.95 gm. protein per kilogram) weight gain was interfered with. In order to find out whether the limiting factor at this point was an essential amino acid or some unessential nitrogenous compound a supplement of glycine was added. With the addition of this supplement it was found possible to reduce the protein intake of 4% of the total calories (1.27 gm. per kilogram) without evidence of impaired nutrition, although such developed if it were lowered beyond this. Normal performance at this low level of protein was sustained for many weeks, as long, in fact, as the experiment was continued. It is thus apparent that the limiting factor in a low-protein diet when the protein is cow's milk is "unessential" rather than some "essential" form of nitrogen. Preliminary operations have shown that urea will likewise spare protein under these conditions, although it appears to be somewhat less efficient than glycine.

The possibility of protein sparing by simple nitrogenous compounds which are both cheap and palatable may have applications in feeding programs for the so-called underdeveloped countries.

DISCUSSION

DR. HAROLD E. HARRISON, Baltimore: It's always nice to have someone explode outmoded dogma. In your textbooks it is usually stated that in human milk, which provides 8% of the total calories as protein, the essential amino acids are present, of course, in the required amounts; it is also stated in the textbooks that cow's milk has to be fed at a much higher level of protein intake to provide the essential amino acids in amounts required for growth. In fact, some statements have been made that 50% more protein is required on a cow's-milk than on a human-milk diet.

There has been very little evidence for this. Most of the evidence has come from studies on the rat, and although there are similarities between the human and the rat there are a few differences, too.

I believe the work presented here pretty clearly shows that the amino acids provided in cow's milk are completely adequate at a much lower total protein intake than usually recommended.

One of the arguments against certain types of very high carbohydrate milk mixtures is that such feedings have resulted in protein insufficiency, and I believe that is not correct.

DR. KAYE, Philadelphia: Dr. McCrory, Dr. Caughey, and I found that infants could be maintained in nitrogen equilibrium on as little as 100 mg. N per kilogram per day. The source of nitrogen in these experiments was casein.

Supplementing the nitrogen intake with gelatin led to approximately a 60% retention, indicating a requirement for nonessential amino acids as well as for the so-called "essential" amino acids.

DR. HARRY H. GORDON, Baltimore: These data should provoke some reassessment of our thinking about protein requirements. I wish to take issue, however, with Dr. Snyderman's conclusion that infants will grow well on the level of protein intake used in this study, and with Dr. Harrison's comment that the data provide an explosion of old concepts. One of the limitations of metabolic studies is the fact that they are usually made on only few infants. Extrapolation of results into generalizations about nutritional requirements is a kind of reasoning which once led Dr. James Gamble Sr. to write that metabolic studies had yielded much precise misinformation about nutritional requirements.

DR. FORBES, Rochester, N. Y.: I wonder if Dr. Snyderman has information bearing on the actual protein intake of children who reside in areas where kwashiorkor is common. This is a disease

which is believed due primarily to protein deficiency, and I wonder if information of this sort is available.

Dr. Barnes, Baltimore: I'd like to second Dr. Gordon's word of caution about applying this kind of information to the normal situation, or even to disease. Also I do believe this is an unusually good contribution and a very important one.

Among other considerations which I believe this paper raises is the question of what does happen to essential amino acids when the squeeze is on, so to speak. We have never known, when the squeeze is on, whether the essential amino acids are forced into their essential pathways and are not able to contribute their nitrogen to the general pool, or, vice versa, whether the rates of reaction involving conversion of the essential amino acids to the general amino acid pool are faster than those rates created by essential demands.

This has bearing on an important subject which comes up often in connection with disease, and I believe further light may possibly be thrown on it by what has already been started with isotope experiments.

Dr. Robert L. Jackson, Columbia, Mo.: I should like to ask Dr. Snyderman as to the linear growth of the infants in relation to their weight growth during the short course of this study.

Dr. Selma E. Snyderman: I want to thank everybody for their comments. I don't believe I can answer all at this moment. We are not advocating that all infants be fed on this low-protein intake. We have simply demonstrated that these two infants, under this particular set of circumstances, were able to do well on the described diet.

As to the question of kwashiorkor, I can't give you an exact answer as to the nitrogen intake. However, these children are older than the children we had to deal with.

That closes what I have to say.

Study of a Child with Sporadic Hypothyroidism Associated with a Goiter. Angelo M. DiGeorge,* and Karl Paschkis,* Temple and Jefferson. (Introduced by James B. Arey)

The occasional appearance of a goiter associated with hyperthyroidism in nonendemic areas has been known for many years. It has been demonstrated that these patients fail to elaborate the thyroid hormones as a result of a defect in one of the complex chains of reactions leading to their synthesis. Stanbury has thus far described three different defects of thyroid synthesis in goitrous cretins.

In the first type, radioiodine accumulates rapidly in the gland after administration but is immediately discharged upon oral administration of KCNS. In the second type iodine is bound to form mono- and diiodotyrosine but only limited amounts of thyroxine are formed. In the third type there appears to be excessive formation and release of thyroid hormone precursors. This paper will present data on a patient in whom the defect in synthesis appears to differ from those which have been described previously.

The patient was a 7½-year-old girl with a goiter of 4 years duration. This was not the result of lack of iodine nor of a goitrogenic agent. The only clinical manifestations of hypothyroidism were moderate somatic and mental retardation. Laboratory studies revealed a retarded bone age, elevated serum cholesterol and depressed levels of serum alkaline phosphatase. Serum PBI levels, accumulation of radioiodine in the thyroid and protein binding of I^{131} were all in the hyperthyroid range.

The administration of potassium thiocyanate 24 hours after a tracer dose of I^{131} failed to cause the discharge of significant amounts of radioiodine from the thyroid gland. Only one third of the PBI^{131} was extractable with butanol and identifiable chromatographically as thyroxine. Bioassay of the serum using the stasis tadpole technique failed to reveal any TSH activity.

Without therapy, certain studies were repeated one year later and found to be essentially unchanged. Therapy with thyroid hormone resulted in improvement. These findings suggest that the patient's thyroid liberates a biologically inactive iodinated protein in the blood. The significance of the findings as related to previously described defects of synthesis of thyroid hormones will be discussed.

DISCUSSION

Dr. William A. Reilly, San Francisco: These cases are becoming reported more frequently, and I think they deserve a good deal of careful study, and I would urge that the people who have an opportunity to study these patients do biopsies and if possible thyroid slice studies.

We have followed a number of them in San Francisco over a period of years. About two years ago here, I reported that in some of our cases we were finding an excessive amount of mono- and diiodotyrosine in radiochromatograms of the blood plasma. One interesting child, who did not have a goiter, excreted 50% of the test dose of I^{131} in 48 hours; some mono- and diiodotyrosine were found in the radiochromatograms of stools and urine. This was a surprise; we postulated then that something happened in the liver disturbing the usual normal degradation of thyroxine.

There are variations of this disturbance. I like to think of this form of thyroid disease as one that is genetically conditioned, since it runs in families. It is another instance of enzyme disturbances which is being demonstrated more and more.

I should like to ask Dr. DiGeorge if he would agree with me that this girl, having an enlarged thyroid, was her own best biological test. I'm sure that you would find hypoplasia areas in the gland and that she was a better biological test than the tadpole.

DR. ROBERT L. BRENT, Walter Reed Hospital: I'd like to inject a note of caution in the use of some of these isotopes in the pediatric age group. I just did some quick calculations on the dose that this child received. It was a 200 microcurie dose, which, in rodents, would produce complete obliteration of the thyroid with a very low iodine uptake. With an uptake of 64% of 200 microcuries, giving a generous allowance of 30 gm. to the weight thyroid—which would be adult size—this child received 400 to 600 to the thyroid.

Now, there has been some reports in the literature about the effect of irradiation on the production of thyroid carcinoma. True, the people who recommend caution have little to prove the need for caution, since radioactive substances have been used such a short time in the pediatric group, but, if other methods can tell us the same results, I think we ought to consider other means of measurement.

If you are administering a dose of 200 microcuries, the difference in uptake between 10% and 60%—which you can't predict until you determine the uptake—makes quite a difference in the dose that the thyroid receives.

Finally, I am not saying that the dose you gave was dangerous for I do not know, but you are on less firm ground in saying that it was not potentially hazardous.

DR. ANGELO M. DIGEORGE: I should like to thank the people who commented.

We agree with Dr. Reilly that there appears to be an increase in so-called goiterous cretinism, or hypothyroid persons and enlarged thyroids, but whether this is actually an increase in incidence or whether it is because of the advent of newer methods of study and the considerable amount of interest in this field—so that we are just looking for these patients more and studying them a little bit more intensively—I don't know.

The question of TSH assay is a long and involved one which I should like to discuss at length but don't have time to do so. The fact that there is an enlargement of the thyroid does not necessarily mean that at that particular moment there is an elevated amount of circulating thyrotrophic hormone.

I agree with the comment concerning the care of administration of I^{131} to infants and children, and we certainly abhor the indiscriminate use of radioiodine. In this particular patient, it certainly was not necessary to do radioiodine uptake or chromatographic studies. All we had to do was give this patient thyroid; but in order to study the physiological mechanisms of some of these patients, I don't know how we can get around the use of radioiodine.

Before this patient was given 200 microcuries of radioiodine the potential dangers were carefully considered by the departments of Radiophysics and Radiology. However, it was decided that information that could be gained would outweigh the disadvantages.

Aminoaciduria as a Manifestation of Renal Tubular Injury in Lead Intoxication. J. JULIAN CHISOLM JR.,* Johns Hopkins. (Introduced by Harold E. Harrison).

The occurrence of aminoaciduria, glycosuria, hypophosphatemia with hyperphosphaturia, and rickets in a child with lead intoxication has been previously reported. The purpose of this paper is to report studies undertaken to ascertain the frequency and extent of these biochemical changes in childhood lead intoxication, and to compare the findings in plumbism with those which occur in vitamin D deficiency rickets, cystinosis, and hyperparathyroidism.

The urinary amino acid excretion pattern has been carefully studied by various paper partition chromatographic techniques in 21 children with acute lead intoxication. In 10 of these patients serial studies have been made during the acute and convalescent phases of lead intoxication. These serial studies include determinations of the urinary excretion of amino acids, coproporphyrin, phosphate, citrate, and glucose; the concentrations of amino acids, calcium, phosphate and citrate in serum; the concentration of lead and glucose in whole blood; and serial radiologic studies of long bones. Similar studies were obtained in patients with vitamin D deficiency rickets, cystinosis, and hyperparathyroidism.

The aminoaciduria seen in acute lead intoxication is a generalized one. At its height chromatographic studies of urine reveal marked increases in glutamine, serine, glycine, threonine, alanine, histidine, and lysine; moderate increases in valine, tyrosine, ethanolamine, and alpha-amino-n- butyric acid; less consistent increases in leucine, iso-leucine, phenylalanine, glutamic acid, aspartic acid, alpha-amino-adipic acid, and cystine. In five patients the concentrations of the various amino acids in serum ultrafiltrates were found to be normal by semiquantitative estimation from two-dimensional paper partition chromatographs. The relative concentrations of these amino acids in urine appear to parallel their relative concentrations in the serum. From these studies it is concluded that the aminoaciduria of lead poisoning represents a biochemical defect in the renal tubular reabsorption of amino acids. The pattern of the amino acids found in the urine is the same as that found in vitamin D deficiency

rickets, which, likewise, has been shown to result from a similar disturbance in renal tubular function.

Hyperphosphaturia, hypophosphatemia, hypercitraturia, and "glycosuria" were found to be rapidly reversible changes present only during the acute phase of lead poisoning in the most severely ill patients of this series. No significant changes in serum calcium concentration were noted; nor was radiologic evidence of unequivocal rickets found in any of the children of this series.

The intermittent presence of a reducing substance in the urine in lead poisoning is well known. Previously, this reducing substance has been identified as glucose. In five or six acutely ill patients in whom reducing substance was found in the urine, two reducing carbohydrates, glucose and fructose, were identified by paper chromatography. Blood sugar concentrations were normal in these patients.

The biochemical changes described were found to be frequent in acute lead intoxication, to be reversible and to be correlated (a) with the clinical severity of the intoxication, (b) with alterations in whole blood lead concentration, and (c) with changes in urinary coproporphyrin excretion. Following treatment with edathamil calcium-disodium the aminoaciduria disappears as does excessive urinary coproporphyrin output. The evidence obtained suggests that lead produces renal tubular injury which results in an interference with the renal tubular reabsorption of phosphate, amino acids, and glucose. This functional lesion is reversible. The findings provide further evidence of an interrelationship between the renal tubular mechanisms for the reabsorption of phosphate, glucose, and amino acids.

DISCUSSION

DR. CHARLES A. JANEWAY, Boston: I'd just like to see if I can tempt Dr. Chisolm to speculate a little further; when all the heavy metals and even calcium in excessive quantities produce renal tubular damage, has he any theory to explain the observations which he has shown us so beautifully?

DR. PHILIP L. CALCAGNO, Buffalo, N. Y.: I'd like to ask Dr. Chisolm whether or not he has any information that would tell us whether the distal tubules are also affected, that is, urine pH and osmolar concentrating capacity.

DR. ANGELO M. DIGEORGE, Temple Univ. Med. School: I should like to ask Dr. Chisolm how often patients with hyperparathyroidism demonstrate aminoaciduria.

We have recently had the opportunity to study a 6-months-old infant with primary hyperparathyroidism who did not demonstrate aminoaciduria.

PRESIDENT ZUELZER: I'd just like to remind you that the morphology of this lesion was described a long time ago at Johns Hopkins by Blackman. It's a very useful tool.

DR. JULIAN CHISOLM JR.: I don't know that Dr. Janeway can tempt me to speculate, because I'm afraid it would be pure speculation. We have no reasonable explanation.

I might point out that these changes have been produced by Dr. Harrison experimentally with oleic acid, but we cannot speculate.

In answer to Dr. DiGeorge, I know of one further case of hyperparathyroidism, I believe, in an adult, which is in a small note by Fanconi in a large discussion. I know nothing other about it than that we have not been able to pin down any changes in the distal tubules.

I might point out that this lesion is rapidly reversible. These patients are acutely ill, but they recover so rapidly that there is little chance left to study them. We do see what we believe to be losses of sodium in the urine, but our treatment tends to produce these things, so we prefer not to give any interpretation of that.

Reduced Uroporphyrin III as a Direct Intermediate in Heme Biosynthesis. ROBERT A. ALDRICH, RICHARD A. NEVE,* ROBERT F. LABBE,* Oregon.

Uroporphyrin and coproporphyrin have long been suspected of playing an intermediate role in heme biosynthesis, but direct evidence for this belief has unfortunately been lacking. Within the past year, Rimington (*Endeavour* 14:55, 1955), and also Shemin and others (*J. Biol. Chem.* 215:613, 1955) have presented theoretical considerations which suggested that these tetrapyrroles were not in the main pathway of heme biosynthesis, but instead might be oxidation products of other heme precursors or porphyrinogens. Colorless enzymatically produced substances which undergo autoxidation to uroporphyrin and coproporphyrin have been identified by Bogorad (*Science* 121:878, 1955) and Granick (Absts., 128th Meeting, Am. Chem. Soc., p. 69, c Sept., 1955).

The experiments to be presented provide the first direct evidence that reduced uroporphyrin III is an intermediate in heme biosynthesis. Uroporphyrin III, isolated from the feathers of the Turacus bird, was reduced with sodium amalgam. This colorless non-fluorescent product reoxidizes in air to uroporphyrin III, as shown by its absorption spectrum. Addition of the reduced uroporphyrin III to an in vitro lysed duck blood system was found after incubation to yield increased levels of uroporphyrin, coproporphyrin, and protoporphyrin. Under identical conditions but with the addition of tracer Fe^{59} the radioactivity of hemin was increased approximately 10 times, indicating increased biosyn-

thesis. To further test this evidence that reduced uroporphyrin III is a direct intermediate in heme biosynthesis, an isotope dilution experiment was performed using a direct precursor of heme, glycine-2-C^{14}, under the same conditions. Exogenous reduced uroporphyrin III in very small amounts (0.15-0.29 micromoles) decreased the C^{14} incorporation of glycine into heme approximately 50%, and, therefore, must be in the main pathway of heme biosynthesis. These and other experiments in progress using different tetrapyrroles indicate that a new series of reactions involving reduced tetrapyrroles must probably be added to the known steps in heme biosynthesis.

Clinical states of anemia characterized by inhibited hemoglobin synthesis and abnormal concentrations of free porphyrins in circulating erythrocytes may reflect disturbances at one of the above steps. The data supporting these studies will be presented and discussed as it may apply to some of the diseases of childhood.

A Quantitative Study of Absorption of Food-Iron at Various Ages. JEANETTE SCHULZ* and NATHAN J. SMITH, University of California.

Absorption of food-iron has been studied quantitatively in normal children and in iron deficient subjects.

The iron of hens' eggs has been tagged in vivo by injecting Fe^{59} into laying hens. The Fe^{59}-containing eggs were fed alone and as part of a normal breakfast to 30 fasting normal infants and children and 12 adults. Quantitative stool collections were made until fecal excretion of radioactive iron was less than 1% of the total ingested dose. Stools were analyzed for their Fe^{59} content and the percentage of the isotope absorbed was determined. The total iron content of eggs from the injected hens was determined chemically and the amount of iron assimilated by subjects in the various groups was estimated. These results are compared with similar observations in four deficient children.

Fe^{59} as sodium iron pyrophosphate has been added to cereals commercially available for infant feeding. The labelled iron was added in a manner identical to that used in routine manufacture of the cereal. The cereal containing Fe^{59} was fed to normal infants and to a group who were found to be iron deficient.

From these studies it has been possible to evaluate iron absorption as a function of age, iron depletion, and food course. More precise concepts of normal iron demands and the possible dietary sources to meet these demands have been gained by these studies.

DISCUSSION

DR. HUGH W. JOSEPHS, Baltimore: This is a perfectly beautiful piece of work and answers very clearly, I believe, the question of the absorption of iron and its probable adequacy during infancy.

The thing I should like to remark is that there is a point in the iron intake below which absorption apparently does not take place. This amounts to about one-tenth of a milligram per kilogram of body weight. It would be well therefore to know what the total amounts of iron in these dietaries were, because, if one takes this apparent basic requirement into account, the percentage of absorption becomes somewhat higher on higher intakes. I noticed that this was true in some of the determinations, that the amount of absorption on the enriched cereals was higher than those on milk.

It is very difficult in milk feeding to get beyond this basic range, and I believe that's partly why milk is such a poor source of iron. Once you have given enough milk or unenriched cereal to get beyond this range, the absorption on milk may be up to 35% or 40%.

With beef, which is a very good source of iron, the same thing is true. I should also like to ask if any vegetables grown in hydroponic solutions containing radioactive iron have been used.

DR. IRVING SCHULMAN, New York: I believe this is a splendid study, and presents data which we have been lacking, and have been necessary for a long time. I believe it shows that we cannot take data from adults, and apply them to children. This is something that most of us have realized, since if this were so practically every child would have iron deficiency anemia by the time he was 2 years of age.

I believe the data casts doubt on the need for routine iron supplementation by mouth or injection without adequate clinical evidence of need.

I should like to ask whether the authors have as yet studied the influence of adding ascorbic acid to the food, whether they measured the absorption of ferrous iron and medicinal iron, and have studied the absorption iron in those children whose iron stores are normal or even excessive as in infection and hemolytic anemias.

DR. ALFRED H. WASHBURN, Denver: May I express my puzzlement over an observation that we have made in following our infants and small children along in our study in Denver—a puzzlement that is now much larger in my mind after hearing this delightful presentation of Dr. Schulz. I will end by asking a question.

We have been trying to analyze the relationship over a period of months and years between the dietary intake of various substances and the resulting picture in the infant's blood. We have been particularly interested in relationship of the intake of iron in various forms to the hemoglobin levels.

So far, at least, we appear to have absolutely no relationship between the iron contained in the reenforced baby cereals and the hemoglobin level, and yet we have a fairly good relationship with the intake of iron in almost everything except the cereals.

As you can understand, I'm a little skeptical about Dr. Schulz's "plug," shall we say, for iron-enforced cereals, and I wonder if she has any proof as to whether the iron in reenforced cereals is actually used in the production of hemoglobin.

DR. LOUIS K. DIAMOND, Boston: I should like to ask one question and take this opportunity to make one observation. We have often tried to compare the diets of children with marked iron-deficiency anemia, with those that have no anemia, and it is frequently difficult to see very much difference. Both groups may have been fed large amounts of iron-poor foods. I wonder if Dr. Schulz and Dr. Smith have had the opportunity of comparing the iron deficient children with respect to their ability to absorb iron, and whether an intrinsic or inherited or congenital factor of poor iron absorption plays a role in one child, as compared with normal controls.

DR. GEORGE M. GUEST, Cincinnati: Following Dr. Diamond's remarks on normal controls I should like to emphasize the fact that seemingly normal infants grouped for control studies may differ greatly in their individual metabolic behavior. It is well recognized that the infants most prone to develop iron-deficiency anemia are prematures, twins, and infants born to mothers who are anemic during pregnancy. But there are many physiologic factors in the seemingly "normal" infant that may influence considerably the absorption of iron, and its metabolic turnover, within a wide range of variability. First-born infants display a significantly lower tendency to develop even mild degrees of anemia than their later-born siblings. Thus, birth order is one item in the background of infants taken as "control" subjects that should be considered in analysis of comparative data such as those here discussed.

DR. JEANETTE SCHULZ: I should like to thank all the commentators.

In answer to Dr. Josephs, the total quantity of food fed to these children did not differ specifically in bulk. However, the iron content of the food certainly did differ. There was much more iron in the iron-enriched cereals than in any of the other foods that have been fed.

However, the mean absorption rate for children under 26 months of age given cereal iron and the average absorption rates for iron from other foods, limiting the group to 26 months of age, shows no significant difference.

Dr. Schulman, I have a note here about infection, but don't specifically remember the question.

DR. SCHULMAN: I asked whether in conditions in which the iron stores known to be not depleted, but rather full, whether there is any difference in the absorption of these food iron preparations.

DR. SCHULZ: We have not yet had a chance to study abnormal children.

To Dr. Washburn, I should like to say that we cannot correlate per cent of iron absorbed with hematological findings or the history of the child. In normal children, not more than 1% of the absorbed radioactive iron could be found in the circulating red blood cell mass in a two-week period. This was true whether the administered food was cereal or egg or milk.

Our iron-deficient group has not been completed. We have to date about seven iron deficient children who have been studied. Their absorption rates have not differed quantitatively from those of our "normal" controls. However, each one of them has demonstrated a rapid uptake of the radioactive iron into the hemoglobin, which is measurable in the red blood cell mass.

We would agree with Dr. Guest on the importance of histories, and what has happened in the child in regard to the child's iron stores and to his iron demands and requirements in the first two years of life. In all these children, we tried to collect our controls as well as we could, limiting our group to healthy children who had a normal birth weight. Prenatal histories were negative. None were twins, and none have had other than upper respiratory infections since birth.

New Deficiency Syndrome Occurring in Infancy. M. E. LAHEY and W. K. SCHUBERT,* Cincinnati.

Interest in the metabolism of copper was aroused some 30 years ago when Elvehjem and co-workers demonstrated that rats fed exclusively on milk develop an anemia which is responsive to iron therapy only after the addition of copper.

Though a similar deficiency might be expected in infants, a well documented, naturally occurring deficiency of copper has never been reported in the human. Indeed, an attempt to produce such a deficiency in two infants met with failure.

Should a deficiency of copper be found in the human infant, it might be expected to be accompanied by hypocupremia, by anemia, and probably by a disturbance in the metabolism of iron.

The present report is concerned with a syndrome encountered in infancy in which there is in fact hypocupremia, anemia, and hypoferremia, and in addition a disturbance in the metabolism of protein.

The five affected patients, 6-15 months old, exhibited marked pallor (with hemoglobins ranging from 2.6 to 5.7 gm. per 100 cc.) and varying degrees of generalized edema (with serum proteins ranging from 3.9 to 5.8 gm. per 100 cc.). Morphologically, the anemia, like that resulting from iron

deficiency, was microcytic and hypochromic and was accompanied by mild reticulocytosis and normoblastic hyperplasia of the marrow. Chemically, the disorder was characterized by hypoferremia, but unlike the anemia of iron deficiency, by a reduction in the iron-binding capacity of plasma as well as by hypocupremia, the latter ranging from 37 to 61 μgm. per 100 cc. Electrophoretic analyses of the serum proteins revealed a reduction in the albumin and gamma globulin fractions. There was no excessive urinary loss of protein, amino acids, iron, or copper.

Response to therapy suggests that (1) there is no defect in absorption or utilization of medicinal iron, (2) the hypoproteinemia is partially restored by iron therapy alone, but completely corrected only after the addition of copper, and (3) that hypocupremia is not secondary to hypoproteinemia.

The observations are tentatively interpreted as indicating that the patients are deficient in both iron and copper.

DISCUSSION

DR. NATHAN SMITH, Los Angeles: We have seen four patients with anemia, irritability, edema, and hypoproteinemia. Hypoferremia and hypocupremia was also present, as described by Dr. Lahey. Observations in our clinical materials has demonstrated one or two points of interest.

Clinical and biochemical abnormalities noted in our patients occurred while they were on optimal diets, which included fruits, vegetables, and meats. These were the diets that the patients ingested while they developed their disease and were the diets which were given to the patients during hospital observation.

The age of onset was from approximately 5 weeks to four months of age. The low serum-copper levels seemed to correlate quite well with levels of serum protein, for when the protein was over 3.5 gm. per 100 cc. the serum copper level was near the normal range.

In our studies balance studies were carried out, with the measurements of phosphorus, potassium, and fat being studied. No negative balances were encountered. Using Fe^{59}-labelled foods we found the absorption of iron to be entirely normal in one patient.

An interesting morphological finding was encountered in examination of the bone marrow from each patient. A rather striking absence of any normoblastic hyperplasia was noted in all four of the subjects studied. This is of interest in as much as copper-deficiency anemia described in animals has been accompanied by a marked normoblastic hyperplasia similar to that seen in iron deficiency and pyridoxine deficiency. Because of the age of onset at which the disease has appeared in our patients, the excellent diets which have been taken while the patients have been observed in the hospital with symptoms of their disease, and the spontaneous recovery of the patients without dietary or medical therapy, we find it difficult to believe that these symptoms, similar to those described by Dr. Lahey, can result from a dietary deficiency or inability to absorb copper or any other nutrient.

Dr. Ulstrom, who has directed out study might be able to tell us of some interesting findings regarding protein metabolism that we have found in our clinical material.

DR. ULSTROM, Los Angeles: The studies in protein metabolism on the infants that Dr. Smith was just telling about reveal that these children, as compared with normal children of comparable age, are incorporating amino acids into the serum proteins at approximately the same rate, when compared on the basis of isotope concentration per molecule of protein.

Since the total protein level is low, this would mean that the actual incorporation rate in a given child with hypoproteinemia is relatively impaired, since we find the destruction rate (or the degradation rate) of albumin and total globulin to be considerably faster in the hypoproteinemic infants—approximately two to three times as fast, in terms of the half life of protein, as in normal infants.

In other words, the rate that they are making the protein is about the same, but since they are degrading it much faster, they should be manufacturing it much faster. They don't, so they remain hypoproteinemic.

From these studies, and also one study which showed that the dietary N^{15} from glycine was excreted at a rate comparable with the normal adult, we conclude that a relatively fast protein degradation rate, and not primarily a failure of amino-acid utilization, is responsible for the hypoproteinemia.

This suggests that the incorporation of new amino acids into the serum proteins is going along at probably close to a normal rate, but that the protein, once formed, in some way is abnormal, or the catabolism forces, or the anti-anabolism—whatever you will—are increased, so that the protein just doesn't stay around as long.

These children have been studied for evidence of inflammation and adrenal cortical hyperactivity, and none has been found.

We feel that some intrinsic metabolic error produces this nutritional-like syndrome, but, as Dr. Smith mentioned, the dietary histories as well as these studies we performed lead us to feel that a dietary basis is not the primary etiology here.

DR. WALTER HEYMANN, Cleveland: Just recently, hypoalbuminemia has again been thought to be the cause of the nephrotic hyperlipemia. I should like to ask Dr. Lahey whether hyperlipemia was noted in these infants. It would be of great interest to know that, in that this type of hypo-

albuminemia would not be due to the loss of albumin into the urine.

Dr. Charles Brubaker, Los Angeles: At the Los Angeles Childrens Hospital we have been interested in the occurrence of hypocupremia in certain cases of iron-deficiency anemia in infants. Four months ago, at the Western Society for Clinical Research, Dr. Phillip Sturgeon and I reported the results of our studies on four such cases. Subsequently we have observed a fifth case.

The cases observed in our Clinic and those presented by Dr. Lahey are parallel in nearly every respect. The dietary histories, age of onset, physical findings, hematologic and blood chemical values reported by Dr. Lahey are virtually identical with those we have observed. Our evidence, likewise, suggests the disorder is a previously unrecognized deficiency syndrome.

On the other hand, the patients which Dr. Smith of the University of California at Los Angeles has just described differ significantly in dietary histories, age of onset, and response to treatment, and, if further studies confirm their observations, it is possible their cases represent a different disorder.

Another point of interest—specific literature references on the occurrence of hypocupremia in iron-deficiency anemia are not available. Also, it is generally felt that serum-copper concentration is increased in iron-deficiency anemia. However, we have made an extensive review of the literature and have noted the occasional observation of an abnormally low serum-copper concentration in so-called nutritional anemia. Instances of such observations are found in the reported data of investigators in Sweden, the Philippine Islands, Switzerland, and Holland. The authors of these reports have not realized, or at least have not commented on, the significance of the low copper concentrations.

On the basis of our studies plus the data in the literature, and now the findings Dr. Lahey has presented, we feel hypocupremia does occur in certain infants and that this is one manifestation of a nutritional deficiency.

Dr. T. Shepard, Seattle: I'd like to ask two questions. Dr. Van Wyk has studied copper deficiency in dogs and has found rather extreme osteoporosis in these dogs and has postulated that it might be a tyrosinase deficiency—I should like to ask if you know anything about the tyrosinase in these patients, or the calcium deficiency?

Dr. W. G. Klinberg, St. Louis: I should like to add a note of question to this.

We recently have been in the process of studying a child similar to this with hypocupremia whom we were unable to correct by iron alone, and we were unable to correct with copper alone, but with a combination of both copper and iron together we were able to correct both the hematologic and the hypocupremic aspects.

I wonder from what has been said whether spontaneous remissions of this sort may have been seen before; yet I can't help but feel that copper plays a really important part in this whole picture.

Dr. Alex J. Steigman, Louisville, Ky.: I'd like to tempt Dr. Lahey with an epidemiological question.

In the past decade our programs have been enlivened by two syndromes, the megaloblastic anemia and the vitamin B_{12} convulsion stories, both ultimately shown to be associated with changes in food technology. With others in the room reporting similar situations, one may wonder on epidemiological grounds whether some changes in food technology may again hold the answer.

Dr. Robert Good, Minneapolis: I am very much interested in this report as well as the two presented briefly in the discussions describing similar cases observed in Los Angeles. Thus far, although searching intensively for this syndrome, we have not observed any such case in Minneapolis in recent years. It is, however, at least possible that these cases represent the same syndrome McQuarrie described some 23 years ago.

I wonder whether Dr. Lahey did any studies to define the immunological capacity of his patients. I wonder, further, whether Dr. Lahey's cases were followed long enough to determine whether the gamma globulin metabolism spontaneously returned to normal, as appeared to be the case in Ulstrom's experience.

Dr. M. E. Lahey: I should like to answer Dr. Heymann's question first, and say that at least one of the patients had no hyperlipemia.

I can't entirely reconcile the differences between the patients we studied and those that Drs. Smith and Ulstrom in California studied. I believe Drs. Brubaker's and Sturgeon's and ours are very similar. I wonder whether Drs. Smith and Ulstrom may not have something different.

At the present time, in answer to Dr. Shepard's question, we are aware, of course, of the fact that both iron and copper enzymes are important in the metabolism of tyrosine, and we are studying the urine of these patients for tyrosine derivatives.

I do know that in the copper-deficient swine we studied in Salt Lake City the animals excreted more tyrosine derivatives than did the normal animals. Whether this has a bearing on the hypoproteinemia and changes in the electrophoretic patterns of these infants remains to be seen.

In respect to the other questions by Dr. Shepard, the calcium, phosphorus, phosphatase were perfectly all right in one patient. In two an examina-

tion of the skeleton has revealed osteoporosis, as in the dogs that Dr. Van Wyk studied.

Dr. Klingberg, at the present time we have two additional "copper-deficient" infants in Cincinnati, both of whom have been treated with copper first to see whether there will be any rectification of the hypoproteinemia that exists; this is our first opportunity to do so, and I can't answer your question.

I believe that Dr. Brubaker and Dr. Sturgeon have administered copper to one such infant, and failed to see, as you did, any correction in the hypoproteinemia until iron was also added.

Dr. Steigman, one possible answer to your question is this: Dr. Wilson, who is in the audience, believes that the use by industry of stainless steel, because it is cheaper and easier to clean, has rather largely abolished the copper pipes and copper kettles, and may have resulted in lower copper contents of food now than there have been in the past.

We have analyzed only one sample of milk in Cincinnati, and found that it contains only 140γ of copper per liter, which is as low as we could make milk deficient in Salt Lake City.

Dr. Good, we have done no specific immunologic studies. However, we do know that just as these patients are hematologically corrected, the gamma-globulin level is very promptly corrected, as was not perhaps shown to the best advantage in the slide exhibited earlier. However, in one such patient—to cite always the best one—we have seen the gamma-globulin level rise from 80 mg. to 800 mg. in the space of just two or three weeks.

Multiple Plasma Protein Deficiencies in Certain Disease States. DAVID GITLIN, WALTER H. HITZIG,* I. HERBERT SCHEINBERG * and CHARLES A. JANEWAY, Harvard.

It has been recognized for some time that certain disease states may result from hereditary or acquired defects in plasma protein metabolism. Thus a hemorrhagic tendency results from deficit fibrinogen synthesis and an increased susceptibility to severe bacterial infection is the consequence of an absence of serum γ-globulins. In this study an attempt was made to determine the extent of the metabolic defect in two of these disorders: (1) both congenital and acquired agammaglobulinemia and (2) hepatolenticular degeneration or Wilson's disease.

The diffusion and interaction of antigens and antibodies in agar gels in conjunction with electrophoresis were employed for antigenic analysis of patients' sera. Using both horse and rabbit antisera against human plasma protein fractions, it was shown that at least two other proteins present in normal sera besides γ-globulin are deficient in agammaglobulinemic sera. Likewise at least one other normal protein besides ceruloplasmin is deficient in sera from patients with Wilson's disease.

Since, in agammaglobulinemia, the defect in γ-globulin synthesis is due to an absence of plasma cells, one may speculate that the plasma cell is the source of the β-globulins as well as the γ-globulins noted to be absent in agammaglobulinemia. Thus, the absence of plasma cells means the lack of a given group of enzyme systems necessary for the synthesis of a specific group of proteins. In Wilson's disease, the cellular site of the enzymatic defect is not known; however, it would appear that the hereditary defect may not involve a single specific enzyme system but rather groups of specific enzymes necessary for the synthesis of several proteins. It is, of course, possible that a single enzyme system essential for the functioning of several synthetic systems could be lacking. The demonstration of multiple synthetic defects in these disorders may make it possible to detect the heterozygous state in these diseases and may provide a new approach to the study of protein synthesis.

DISCUSSION

DR. GOOD, Minneapolis: This very interesting report is most provocative to us.

As you all know, we have thought that these children with agammaglobulinemia have an isolated γ-globulin deficiency as well as a complete or virtually complete immunological unresponsiveness. The fact that the other serum proteins in these patients are present in normal concentration has been concluded from salt fractionation studies as well as free and zone electrophoretic analysis. Wolfson, however, has pointed out that a deficiency in the B_2 globulin fraction may also occur, and from the immunological studies this is as it should be, since the isoagglutinins and certain other antibodies which are absent in these patients travel electrophoretically primarily in the B_2 globulin fraction.

Recently Dr. Henry Kunkel, of the Rockefeller Institute, has approached this problem in a somewhat different way. He has found, in confirmation of the studies of others, that antibody-containing proteins are divisible into at least two fractions on ultracentrifugal analysis—the component which sediments rapidly in the centrifuge and is referred to as the S-20 fraction and the lighter component which sediments more slowly and is referred to as the S-7 fraction. From Kunkel's study of the serums of our cases and several of his own it would appear that both antibody-containing protein fractions are regularly absent in agammaglobulinemia. It is possible that the heavy fraction absent in agammaglobulinemic serum could be the same as one of the unidentified fractions shown by this study to be absent in agammaglobulinemic

serum, since I believe Kunkel's work establishes the immunological independence of these two antibody-containing protein fractions.

DR. IRVING SCHULMAN, New York: This concept finds interesting confirmation if one studies children with congenital hemorrhagic diseases. We have found that in certain children not one but several coagulation proteins may be lacking. Of greater significance perhaps have been recent reports concerning families with true hemophilia. In some families it has been found that while some of the males have severe antihemophilic globulin deficiency, close relatives, also with severe hemorrhagic disease, may have normal antihemophilic globulin but marked deficiency of related factors such as plasma thromboplastin component (PTC). One gets the impression that synthesis of these various factors may be determined by the same gene.

DR. WALTER H. HITZIG: I believe we should thank these two speakers, and I have nothing to add.

Studies on Destruction of Red Blood Cells by Canine Autoantibodies in Normal Dogs and in a Dog with Naturally Occurring Autoimmune Hemolytic Disease. GERALD MILLER, FRANK W. FURTH,* SCOTT N. SWISHER,* and LAWRENCE E. YOUNG,* Rochester.

Extensive studies have documented a naturally occurring form of autoimmume hemolytic disease in a dog. The canine disorder is an exact counterpart of the disease occurring in human beings, manifested by profound anemia, spherocytosis, autohemagglutination and agglutinability of the red blood cells by antiglobulin (Coombs) serum. Temporary remission following administration of corticotropin (ACTH) was accompanied by qualitative change of the panagglutinin in the dog's plasma and an increase in titer of the panagglutinin.

Exchange transfusion permitted collection of plasma with high content of panagglutinin. Effects of transfusion of this plasma were studied in four experiments involving three normal recipient dogs. In vitro, the panagglutinin strongly sensitized recipient animals' erythrocytes for the antiglobulin test. Following transfusion, the recipients' cells were not sensitized for the antiglobulin reaction, but coating of these erythrocytes could be demonstrated by loss of ability to react in vitro with samples of the plasma infused. These "blocked" cells showed sphering and increased osmotic fragility. Their life span as determined by Cr^{51} survival was shortened in only one of two normal dogs, although in both dogs the spleen was present.

Studies on the diseased animal and normal recipient dogs suggest that spherocytosis and hemolysis may be conditioned by factors other than the amount of antibody demonstrable on the cells or in the plasma, and that the "autoantibodies" of the canine disease can initiate hemolysis in normal animals. Although the actual mechanisms of hemolysis initiated by these antibodies still await elucidation, it seems clear that these mechanisms are operative in normal dogs transfused with plasma from the diseased dog.

DISCUSSION

DR. DIAMOND, Boston: I'd like to compliment Dr. Miller and his associates on this beautiful study of a single case. It shows, as we all know, the amount of information that can be gotten through such a study, as compared sometimes with statistics from a large number of cases.

It brings up several points of interest. I believe Dr. Miller has answered one question that occurs to many, and that is whether the mechanisms that direct hemolysis in the circulation can account for cells that are damaged, sensitized, or changed in some ways.

Many years ago, Dr. Arthur Abt pointed out the high incidence of circulating erythrophagocytes in erythroblastosis fetalis, which may be a mechanism of the removal of cells, as, for example, ABO erythroblastosis, which does not give a positive Coombs test, but a hemolysis does develop.

Dr. Zinkham, of Baltimore, showed some time ago that sensitizing cells in vitro produces a change which allows a high percentage of erythrophagocytosis to develop.

One point, I believe, that Dr. Miller's study brings out very well is that the failure to demonstrate a positive Coombs test in a possible acquired hemolytic anemia does not render this diagnosis impossible, and there are many patients, especially children with mild hemolytic anemia, that do not have positive Coombs tests, and yet destroy the blood more rapidly, as judged by the development of anemia after infection, usually within a few weeks—which is probably hemolytic, and yet gives none of these criteria that we look for in true, acquired hemolytic disease.

I believe such studies as Dr. Miller and the others have done will point the way to mechanisms other than the positive Coombs tests.

PRESIDENT ZUELZER: I should like to ask some questions of Dr. Miller.

If I understand correctly, the animals that were recipients of this serum also showed cytosis; yet some showed no demonstrable hemolysis and others did.

I wonder if you would comment on that in view of the relation to the role of the spleen.

My other question is somewhat related to the one that Dr. Diamond asked: Did these Coombs-negative blocked cells give a positive reaction either

with a Coombs test or directly when treated with the cells.

DR. VICTOR C. VAUGHAN, Philadelphia: I'd like to ask Dr. Miller if he had any opportunity to test cells giving a negative Coombs test for their possible autoagglutinability in colloidal media such as canine or human serum.

DR. GERALD MILLER: Thank you, the discussants, and Dr. Diamond particularly, for encouraging the study of a single case.

It is agreed that failure to demonstrate a positive Coombs test should not be held as a criterion for a statement that a child or adult does not have an acquired hemolytic anemia.

In answer to Dr. Vaughan's question, we did suspend the cells of these normal recipient dogs in normal dog serum, the only colloidal medium that we worked with, in an effort to demonstrate that the cells were sensitized. No agglutination was observed using this test.

Handling dog cells is a little tricky, and we have not been able to standardize a method for using enzyme-treated dog cells.

Dr. Zuelzer, in answer to your question about the role of the spleen, we were astonished that the dog whose red blood cells showed normal survival, actually had gotten (on a relative weight basis) a bigger dose of antibodies and showed a greater increase in osmotic fragility of the erythrocytes.

We were moved to explore this dog by laparotomy, to make sure that he had a spleen—and he did.

We can't even do any reasonable speculation, except in the bar, about what went on in this dog, and we are unable at present to offer a satisfactory explanation for the apparent normal survival of the affected red cells in the presence of an intact spleen.

In Vitro Evaluation of Nephrotoxic Sera in Experimental Nephrosis. MICHAEL B. ROTHENBERG,* ABRAM B. STAVITSKY,* and WALTER HEYMANN,* Western Reserve. (Introduced by William M. Wallace)

It has been shown that the renal disease produced in rats by the intravenous injection of nephrotoxic sera (NTS) obtained from rabbits simulates the nephrotic syndrome as it is observed in infants and children. The treatment of rabbits with rat kidney suspensions does not, however, always yield potent NTS. Biological assay has thus far been the only available method for testing these NTS. We have therefore attempted to adapt a hemagglutination test, as described by Boyden and modified by Stavitsky and by Adler, to the in vitro evaluation of the nephrotoxicity of anti-rat-kidney sera obtained from rabbits.

Results of 81 determinations on 43 nephrotoxic sera and 10 control sera which included normal sera, rabbit anti-egg-albumin sera, rabbit anti-bovine γ-globulin sera and rabbit anti-diptheria-toxoid sera, indicate a useful correlation between nephrotoxicity and hemagglutination titer. This method enables a differentiation between the "NTS Negative," "one-plus," and "two-to-four-plus" groups of sera outlined by the bioassay technique.

The application of this method to the detection of antibodies in the sera of nephrotic and nephritic children, using various techniques for preparing human kidney antigen, will be discussed.

DISCUSSION

DR. JOHN M. CRAIG, Boston: Are there any suggestions from the results of the action of the aminonucleocide on human kidney digest for the action of the aminonucleocide in producing a nephrotic syndrome in the living rat?

DR. KURT LANGE, New York: I should like to ask Dr. Rothenberg whether in their test for nephrotoxicity the different degrees of activity of different sera can not be equalized by using somewhat larger amounts of those sera which have a lower activity per milliliter.

As far as the inability of Dr. Rothenberg to find antibodies to kidney in their antigen-antibody test in human cases of acute glomerulonephritis and the nephrotic syndrome is concerned, it should be remembered that in our work and in the work of others antibodies to human kidney were usually not found in the acute cases. Only later did they appear with great regularity and with higher titers when highly sensitive systems were used for their detection. It is possible that the mechanism in these two conditions is as follows: the glomerular apparatus is coated by an antigen (possibly of streptococcal and/or other bacterial or viral origin) and an antibody is formed to this antigen destroying the integrity of the glomerular apparatus. Only subsequent to this destruction antibodies to kidney substance may develop.

I should like to ask Dr. Rothenberg if this will not serve to explain their findings.

DR. MICHAEL B. ROTHENBERG: In answer to Dr. Craig, we have no detailed explanation of why the aminonucleocide might produce nephrosis in the rat. It is suggested from some experiments that have been done in our laboratory that it works in an antigenic fashion, mainly because we have noted a latent period of 8 to 13 days before the disease occurs in the rat. I'm afraid I can't answer you any further.

In the case of the nephrotoxic-negative sera, they are nephrotoxic-negative regardless of the amounts used. As regards sera which were classified as one or two plus by the bioassay method, it's true that by giving larger amounts of a less potent serum a severer disease could be produced.

In answer to your second question, we can only say that two or three of the sera which we used from nephrotic children were from nephrotic children who had had their disease for quite some time, and we would, therefore, assume that the renal damage which you postulate as occurring late should have already occurred in these children.

The Relationship of Sydenham's Chorea to Infection with Group A Streptococci. ANGELO TARANTA* and GENE H. STOLLERMAN,* New York University. (Introduced by L. Emmett Holt, Jr.)

The relationship between chorea minor and streptococcal infections was investigated by means of determination of streptococcal antibodies in patients with chorea. Fifty-one patients with chorea as the only clinical manifestation (pure chorea) were studied. The incidence of elevated streptococcal antibody titers, indicative of recent streptococcal infections, was higher in a group of 30 patients studied within one month from the onset of chorea (73.3%) than in patients studied later (45.4%). This incidence was, however, lower than in a comparable group of patients with other manifestations of rheumatic fever, studied within one month from the onset of the disease (95%).

An analysis of the histories of 55 patients with chorea and other manifestations of rheumatic fever showed that the onset of chorea usually follows the onset of the other rheumatic manifestations. A longer lag period between streptococcal infections and chorea minor than between streptococcal infections and the other commonest manifestations of rheumatic fever is suggested by these studies.

Serial determinations of three streptococcal antibodies were made in 10 patients in whom chorea started more than two months after the onset of another rheumatic manifestation. The possibility of intercurrent streptococcal infection was thereby ruled out. By the time chorea appeared, the streptococcal antibody titers were often low, although they were high initially.

The interpretation is advanced that the relatively long lag period between streptococcal infections and chorea may explain the lack of immunological evidence of recent streptococcal infections in some cases of pure chorea. Some clinical and epidemiological data will be discussed in connection with this interpretation.

Immunological studies of the cerebrospinal fluid in 15 patients with chorea failed to yield information on the pathogenesis of the disease.

DR. BENJAMIN M. KAGAN, Los Angeles: The English and the French have long accepted the idea that some chorea is not due to rheumatic fever. In this country there has been reluctance to accept this concept.

A few years ago we reported that patients with chorea seen during the first three weeks after the onset of the first attack, who had no other evidence of rheumatic fever and who had a normal erythrocyte sedimentation rate at that time, may or may not have similar subsequent attacks of chorea but that these patients showed no evidence of rheumatic fever or heart disease during a six-year follow-up.

A few such patients were studied with serial ASO titers. Some had ASO titers above normal for the age, but none were as high as often seen in rheumatic fever. The rises in ASO titer suggest that Streptococcus infection may be of some importance in etiology, but this does not mean that these patients have rheumatic chorea. It may be that beta hemolytic streptococcal infection may cause chorea in one patient, nephritis in another, and rheumatic fever in still another and that these conditions may be seen separately or together in the same patient. A study of streptococcal infection in chorea similar to Dr. Rammelkamp's study in acute glomerulonephritis may be worth while.

Also, it is possible that some of the approximately 25% of so-called "pure chorea" in this study had low ASO titers, not because of a lag period but because they did not have a preceding streptococcal infection and did not have rheumatic fever.

DR. LEWIS W. WANNAMAKER, Minneapolis: I'd like to raise one point about this paper, and that is, that it is exceedingly difficult to define accurately the onset of chorea. As a rule, the first manifestations of chorea are subtle and may be overlooked for weeks or even months by the mother or the physician. Such insidious beginnings may create a false impression as to when the disease process actually begins. In contrast, rheumatic fever is more likely to have an acute onset. Perhaps the observed difference in the length of the latent periods of these two sequelae of streptococcal infection is more apparent than real.

DR. VINCENT KELLEY, Salt Lake City: I believe that, rather than saying that all these patients necessarily had a preceding streptococcal infection—which, at least, was strongly implied here—we might consider some sort of a compromise between the statements of the speaker and the statements of the first commentator.

We have in the Utah State Rheumatic Fever Clinic a large series of patients that have been followed on prophylactic regimens now for several years. In this group we have had 28 recurrences of rheumatic fever; in every one of those 28, we were able to demonstrate a break in the prophylactic regimen and the existence of a streptococcal infection.

Eight of these patients also had manifestations of chorea, and in these eight patients also it was possible to demonstrate a break in prophylaxis and elevation of ASO titers. On the other hand, we have three patients who have had recurrences of chorea with no other manifestations of rheumatic fever. In these three we were unable to demonstrate a break in prophylaxis, and we could not demonstrate any evidence of streptococcal infection.

DR. ANGELO TARANTA: In answer to Dr. Kagan's question, the factors that are involved in the high incidence of recurrences of rheumatic fever are quite obscure. It is known from some statistical work in Sweden that patients tend to have, in their recurrences, the same manifestations that occurred in the first attack. An organ susceptibility or sensitization may play a role here. Something like this might explain how a patient who develops chorea in the first attack may keep developing chorea and no other manifestations.

We have not tried to make a follow-up study of chorea patients as you have done. Our study has just shown that in cases of definite rheumatic fever that develop chorea, the interval between the onset of chorea and the onset of the preceding rheumatic manifestation may be very long and free from intercurrent streptococcal infections.

These findings are compatible with a streptococcal etiology also in those cases of chorea in whom a low ASO titer is found at the time chorea develops.

In answer to Dr. Wannamaker, we certainly have found mild personality changes that, at times, have been detected with projective psychological techniques, that may precede by weeks and even months the onset of a full-blown choreic attack. It is certainly very hard for us to consider how such a long latent period may occur. It may very well be that changes in the brain start quite soon after streptococcal infection: changes that we are not able to detect.

In answer to the question of Dr. Kelley, we have had a very similar experience in our own prophylactic clinic. We have observed some recurrences of chorea that have occured within the six or eight months after an attack of rheumatic fever. Actually, these are very similar to the cases shown in the slides.

We have not seen in children on prophylaxis followed for two years any new attack of chorea occur beyond this length of time.

I want also to add another comment, that all the patients that I have spoken about are patients with their first attack of chorea. The reason for this is that it is very difficult to evaluate the degrees of choreic activity and to distinguish between exacerbations and recurrences. We have found that some patients with chorea show signs of mild chronic choreic activity, with up and downs in their course unrelated to new streptococcal infections, a situation quite similar to that occurring in "chronic" rheumatic fever.

The Serological Response to Natural Infection with Poliomyelitis Viruses. WILNA A. WOODS* and FREDERICK C. ROBBINS, Western Reserve.

Forty-one patients admitted to City Hospital, Cleveland, with the clinical diagnosis of poliomyelitis were studied by serum neutralization and complement-fixation tests on serial blood samples. In 33 the diagnosis was confirmed by isolation of poliomyelitis virus from stool specimens; in one additional patient the diagnosis was confirmed by serological evidence, although no virus was isolated. Following laboratory investigation seven cases were considered not to represent infections with poliomyelitis virus. Coxsackie B_4 was isolated from two, no virus from five.

Neutralization tests were done by the metabolic inhibition method. Trypsin-dispersed monkey-kidney cells were employed. Complement fixation tests were done by the method of Fulton and Dumbell. The antigens were prepared from infected tissue culture fluids concentrated 10 times. The fluids were concentrated osmotically by dialysis against a solution of polyvinylpyrrolidone (PVP). The antigens appeared to be quite specific, and were not anticomplementary.

All 33 patients from whom virus was isolated were found to have neutralizing and complement-fixing antibodies to the homotypic virus in their sera at some time during the period of the study. The one serologically confirmed case developed only Type 1 neutralizing and complement-fixing antibodies. About half of the patients developed only neutralizing or complement-fixing antibodies to the type of virus isolated from the stool. About a quarter of the patients demonstrated both neutralizing and complement-fixing antibodies to the homotypic virus alone. When heterotypic antibody was present, about one half of the patients showed a significant rise to both heterotypic and homotypic neutralizing and complement-fixing antibodies.

A diagnosis of the infecting strain could be made by the neutralization test in 17 and by the complement-fixation test in 20 patients. In 13 patients the infecting strain could be identified by either test. Six of the seven patients considered not to have been infected with poliomyelitis virus showed no rise in neutralizing or complement-fixing antibody. One, from whom Coxsackie B_4 was isolated, was found to have a significant rise in neutralizing antibody to all three types of poliomyelitis virus. Low levels of Type 1 complement-fixing antibody were present in his sera, but no rise occurred.

The time required for neutralizing antibodies to appear was less than three days after onset of symptoms in all but one case. The highest titer

was achieved within the first month in about half of those cases studied throughout the first year. The homotypic titer remained high after the first year in the majority of the patients.

Homotypic CF antibodies usually appeared during the first week, but slightly later than the neutralizing antibodies. The peak titer occurred during the first month in most cases. After the first year, the titer dropped in 17 cases and remained high in 12.

Fifteen of the eighteen patients in whom heterotypic neutralizing antibodies were found to develop demonstrated these within the first two weeks of illness and were present in all eighteen within the first month. Sixteen of the twenty cases demonstrating heterotypic CF response developed heterotypic antibody within the first month. Much of the heterotypic antibody was without doubt the result of prior infection. However, in certain instances where it appeared transiently it is possible that it represented response to an antigen common to more than one of the poliomyelitis virus types.

In this series the diagnosis of infection with a specific type of poliomyelitis virus could be made serologically in approximately half of the cases. Neither test seemed superior. Isolation of the virus would appear to be the best single test for the diagnosis of poliomyelitis infection.

Occurrence of Gamma Globulin in Human Feces. MURRAY M. LIPTON* and ALEX J. STEIGMAN, Louisville.

Undiluted serum of rabbits immunized with human γ-globulin produces precipitation when brought in contact with human γ-globulin up to dilutions of 1:100,000.

Such serum was added to single lots of aqueous fecal extracts of persons 1 month to 90 years of age who were in the following categories: poliomyelitis patients and their contacts; well persons living at home; others in convalescent homes and hospitals.

Of 48 children less than three years of age, 47 yielded positive reaction for γ-globulin. Twenty of the forty-eight children who were not in any way associated with poliomyelitis had γ-globulin in their stools. In a group of 24 people aged 61 to 90 only 2 of 24 showed stool γ-globulin.

In a study of the fecal γ-globulin content of paralytic poliomyelitis cases, therefore, the children less than 3 years were not included in the tabulation, since when tested all were positive as in "normals" of this age.

In 60 paralytic poliomyelitis patients aged 3 to 15 the stools of 43, or 72%, revealed precipitin reaction with the rabbit antiserum. Of these 60 patients fecal virus was isolated in 42, or 70%. In 26 of those from whom virus was isolated γ-globulin was present in the same stool. In 18 cases where virus was not isolated from the feces, 17 showed γ-globulin in the fecal supernate. Stool specimens taken as early as the second day after onset and as late as 26 days after onset have been positive.

Eight of twenty-one, or 39%, well contacts aged 3 to 12 revealed precipitate. Of the eight γ-globulin positive cases one had fecal virus and two were in families of which the case revealed virus.

The precipitation reaction observed using fecal extracts from children less than 3 years of age suggests that the immunologically naive alimentary tract encounters a successive parade of infective antigens (viral and other) and noninfective antigens to which it may respond with the production of γ-globulin. In polio patients the reaction suggests the presence of γ-globulin in response to alimentary multiplication of a pathogenic virus. Its antibody effect in vitro or in nature, its rise and decline in relation to alimentary-tract infections, its origin and fate require further study.

DISCUSSION

DR. GOOD, Minneapolis: I was very much interested in this paper and the implications from a study of this sort. I have a question, however, concerning method.

How sure are you that you are really measuring γ-globulin in this system?

In our own work with Red Cross γ-globulin using Freund's antigens in the immunization procedure we have found at least four immunologically distinct components. I would be worried that without specially purified antigen you might be measuring protein other than γ-globulin by the method employed.

It is perfectly true that provided appropriate antigenic stimulation the bowel should be a good place for antibody production. If one studies the bowel histologically, one regularly finds a rather marked plasma-cell proliferation. This is especially true in the areas about the Peyers patches and in the appendix where a very striking accumulation of these antibody-producing cells may be found. I have always looked on the plasma-cell accumulation in the bowel as a reflection of the constant effort on the part of this organ to defend itself against invasion by enteric pathogens and toxins.

DR. P. F. WEHRLE, Syracuse, N. Y.: I was particularly interested in the children under the age of 3 years. I may have missed it, but I was curious as to whether those children had either circulating antibodies present or virus isolated at the time of the study. Do you have that data?

DR. ALEX J. STEIGMAN, Louisville, Ky.: It will be noticed from the slides that there was an in-

verse relationship between age and the presence of γ-globulin. One might wonder in attempting to fit this data in with the known age relationship with respect to excretion of polio virus, which Dr. Robbins referred to, whether or not local antibody in the alimentary tract represents a phenomenon which diverges from serum antibody.

Physiological factors relating to age may have a bearing. It is well known that prematures and young infants have relatively low levels of serum γ-globulin, yet all those tested show fecal γ-globulin.

DR. MURRAY M. LIPTON: In response to Dr. Good's question, I can say that we have tested our antisera using electrophoretically pure γ-globulin by the Ouidan technique, and have found only one major component and one minor component.

In regard to Dr. Robbins' question, I failed to mention one item in the presentation and that is, of the 60 persons with paralytic poliomyelitis shown on the slide, 42 of the 60, or 70% of the specimens tested, were positive for virus and 26 of these 42 also showed γ-globulin in their stools.

Of the 18 from whom we could not demonstrate virus, 17 had γ-globulin in their stools. Whether or not there is any relationship, I won't at this time say.

In regard to the last question, of the 47 persons, 27 specimens had come from contacts of cases with poliomyelitis virus. I believe we isolated the virus from all of the 27 cases, but of the 20 that I mentioned none of them came in contact, as far as we know, with poliomyelitis virus. They were from normal children of laboratory personnel, and their stools were taken at home and brought into the laboratory.

The ones in the convalescent homes were children with various illnesses, some were there in relation to feeding problems.

Isolation of Agents Other than Poliovirus in Seasonal Aseptic Meningitis. DR. DAVID T. KARZON, DR. ALMEN L. BARRON,* DR. WARREN WINKELSTEIN JR.,* and DR. SEYMOUR COHEN,* Buffalo.

A clinical syndrome occurred in epidemic form in western New York in the summer of 1955 and was characterized by (1) acute onset of fever, (2) severe frontal headache, (3) nausea and vomiting, (4) pains in the abdomen, limbs, or chest, and (5) signs of meningeal irritation. Transient muscle weakness and reflex changes occurred in a few cases but there was no residual paralysis. One hundred sixty-two viral agents were recovered to date in monkey-kidney-tissue culture from the stool and pharynx of hospitalized patients reported clinically as "nonparalytic poliomyelitis" and from healthy household contacts. In addition, 10 agents were recovered from spinal fluids. Agents were recovered from 75 of 84 hospitalized patients with aseptic meningitis (89%). The virus recovery rate in these patients was as follows: stool 83%, pharynx 58%. Among 59 stool specimens from household contacts, virus was recovered in 30%. No virus was recovered in 16 throat swabs from contacts.

The agents were not neutralized by antisera to poliovirus types I, II, and III. The prototype strains so far studied were not pathogenic for suckling mice and were not neutralized by Coxsackie virus antisera. Over 90% of the isolations, including 7 of 10 CSF isolations, were identified by neutralization test to be enteric cytopathogenic human orphan (ECHO) virus type 6. In addition, three unidentified orphan serotypes were encountered. Neutralizing antibody levels to ECHO virus type 6 in patients, in pooled γ-globulin, and in the normal population were presented. The evidence that these agents were etiologically related to the clinical syndrome of aseptic meningitis was discussed.

During the course of this study, it was found that manipulation of the pH of the medium exerted a marked effect on growth of these viral agents. Maintenance of a pH of 7.2-7.4 during culture favored the growth of the ECHO agents. In addition, the recovery rate of virus from primary patient sources was shown to be enhanced or encumbered by appropriate selection of the buffering capacity in monkey-kidney monolayers.

DISCUSSION

DR. WEHRLE, Syracuse, N. Y.: We have been very much interested in Dr. Karzon's work, inasmuch as we have had a very similar clinical illness in the Syracuse area during the past two years.

During these years, approximately one-third, or slightly less, of the patients referred to the Syracuse City Hospital have been found to have an exceedingly mild nonparalytic illness with symptoms consisting of headache and vomiting, with fever persisting for from one to three days. The physical findings have been limited to signs of meningeal irritation, and the spinal fluid has contained increased cells and protein routinely.

We have isolated agents from this group of patients that appear quite similar to those described. We have been using the monkey kidney cell with Hank's medium, which has not been particularly helpful in the cultivation of these agents, as Dr. Karzon pointed out.

We are quite certain these agents are not polio, and they are not pathogenic for suckling mice.

DR. ROBBINS, Cleveland: Northern New York seems to have experienced a high rate of infection with the ECHO viruses. The experience in other parts of the country can be quite different.

In Cleveland the rate of isolation of ECHO viruses has been low. In a group of 80 patients

diagnosed as poliomyelitis last year, poliomyelitis viruses were isolated from 30%. From another 30% we isolated Coxsackie viruses, mostly Group B, from 15% identified agents presumed to be ECHO viruses, and from the remainder, nothing.

Dr. Karson's isolation of the ECHO agents from the spinal fluid is of great interest and important in indicating an etiologic relationship.

I should like to ask Dr. Karzon what type of cell he is using in his culture and whether there is evidence of any particular cell being more or less susceptible to infection with ECHO viruses.

DR. HEINZ EICHENWALD, New York: I believe Dr. Karzon's demonstration that a rather slight change in the physical and chemical environment of cells leads to a change in susceptibility is of considerable interest.

We have recently been using human amnion cells to attempt to identify various respiratory viruses. In this work we have come across a virus for which we have not yet been able to think up a suitable name, but this particular agent will multiply very rapidly and give high titers in amniotic cells maintained in mixture 199, but if the cells are left in Scherer's solution, which is somewhat less complex, the titers achieved are considerably lower.

In addition, like Dr. Karzon, we have found that the number of primary isolations can differ with different maintenance media even though the cells look alike and act alike, and the pH certainly is not different.

A somewhat similar experience has been obtained using a cell which resembles the HeLa cell. It's an epidermoid carcinoma which, after having been grown in a medium composed of mixture 199 and 10% serum in Hank's medium, will support very rapid propagation of this particular respiratory agent, but when the cells have been grown in 20% human serum and 80% Hank's medium the virus propagation is definitely diminished, even though the same maintenance solution is employed.

DR. DAVID T. KARZON: Dr. Robbins, I'm sorry that I didn't mention that I used the monkey-kidney-cell system for growing these viruses. In our hands it's much superior to the HeLa system. Our pH experiments were conducted in monkey kidneys.

I can answer Dr. Wehrle's and Dr. Robbins' comments about the rate of isolation and the distribution in this way. I believe what happened in western New York in 1955 probably won't happen again in western New York in 1956. We merely sampled one geographical area at one time. The polio season, I believe, was unusual in the history of our Health Department. The paralytic ratio was very low—perhaps 10%, if we knew all the figures—and so we had a true epidemic of nonparalytic polio, or aseptic meningitis. I'm certain that in Buffalo in another year we may find that as many as one-third or one-half of the nonparalytic polios or aseptic meningitis cases are caused by typable polio viruses. The experience with aseptic meningitis in Ontario in 1955 seems to be the same as ours, and the material studied by Dr. Dalldorf also showed that the Troy, N. Y., epidemic was caused by an ECHO virus.

It is interesting to note that when we went back to the isolations recovered from the Buffalo epidemic of 1954, ECHO Type 6 virus was the predominant type.

An Experimentally Developed Rationale for Vaccination of Children Against Influenza. A. V. HENNESSY,* Michigan. (Introduced by Bruce D. Graham)

Studies of the distribution by age of antibody to influenza viruses have shown a remarkable correlation between the type of antibody found now in the sera of children, young adults, and persons over 30 and the antigenic character of strains prevalent during the childhood of each age group. From these data the thesis was derived that the initial infection of childhood with influenza viruses orient the antibody-forming mechanisms so that upon subsequent exposure to strains of influenza virus of varied but related antigenic composition the level of antibody to strains of primary infection is reinforced while serologic response to prevailing viruses may be dampened.

In addition it was pointed out that the decrease in incidence of influenza in older groups correlates with the broad composite of antibodies characteristic of older persons even though low levels of antibody to recent strains are found in their composite. In contrast, the antibody of children is narrower in scope, although high levels of antibody to recent strains are present. Nevertheless, the incidence of influenza is greatest in childhood. It would seem logical then that to afford children maximal protection against influenza it would be desirable to develop in them by vaccination a broad composite of antibodies similar to that found in the more resistant adults.

To delineate and quantitate the antibody response of children to influenza virus vaccines composed of strains representative of what is known of the periods of prevalence of the three major antigenic families of influenza virus, groups of 20-25 children, 4-11 years, were vaccinated with monovalent vaccine containing Swine, PR8, or FM1 strains and with a polyvalent vaccine containing the same viruses. The concentration was 750 CCA units per ml., and that dose was given subcutaneously. Antibody increase was measured by hemagglutination inhibition in sera collected before and two weeks after vaccination.

In children whose initial exposures were influenza A-prime, vaccination with all vaccines resulted in a marked increase in antibody against A-prime strains. Little or no antibody increase

to Swine or PR8 occurred unless the homologous vaccine was given. However, it was found possible to induce satisfactory levels of composite antibody with a single dose of polyvalent vaccine. Therefore, a polyvalent vaccine seems to be practicable and desirable for use in vaccination of children. To determine whether the antibody response of children primarily infected with influenza A-prime could be broadened by experience with Swine and A strains given by vaccination, a group of children previously vaccinated with these strains were revaccinated a year later with a monovalent vaccine containing the Malaya (1954) strain of influenza A-prime. These revaccinated children unlike others responded to the adjuvant vaccine with a marked reinforcement of antibody levels to Swine and PR8 virus.

The findings of this study demonstrate that a broad spectrum of antibodies against influenza virus may be induced in childhood by use of a polyvalent vaccine and suggest that it may be possible to maintain a broad antibody spectrum by subsequent revaccination of children with a single strain. Such a procedure would be expected to afford maximal and efficient protection of these children against influenza.

DISCUSSION

DR. JOSEPH STOKES JR., Philadelphia: I should like to ask Dr. Hennessy a practical question concerning vaccination. I remember that Dr. Michael Sigel, working at the Children's Hospital of Philadelphia, recorded successive epidemics of A-prime influenza at the Lawrenceville School separated by about two years. Not only were the boys not protected who had been previously vaccinated with the usual vaccines containing PR8 and Weiss strains of virus, but the second epidemic caused a higher rate of infection in those boys who had had the disease from the same virus in the first epidemic than in the same age group who had entered the school after the first epidemic. The same situation obtained in the space of only one year in two successive epidemics in New York State. The question is, if the natural disease protects for less than two, or even one, year, how long may one expect vaccines to protect such as Dr. Hennessy is discussing?

DR. THOMAS H. WELLER, Boston: The immunologic doctrine that Dr. Hennessy has described here has been referred to quite succinctly by Dr. Francis as "the doctrine of original antigenic sin." I believe it's appropriate to stress this point, because it's an immunologic principle that probably carries over to a wide variety of other viral antigens. If you will remember Dr. Robbins' presentation, certain of his patients demonstrated dominant heterotypic antibody responses. His findings may well be explained in much the same manner as the findings with influenza virus now reported.

DR. A. V. HENNESSY: In regard to Dr. Stokes' question about the use of influenza vaccine, we have conducted every year field trials with the vaccine primarily in persons of recruit age. We have at times used a single strain, including the FM1 strain, and there has been a protection against influenza A-prime of about four to one.

We have had very few experiences with actual outbreaks in children who have been vaccinated. I cannot explain why these particular children did not get protection if they did get good antibody levels. They may not have gotten good antibody levels, or, as will sometimes happen when they have been inoculated for the first time or have their first experience with influenza virus, they may not develop good levels of antibody.

I agree that the disease is a mild one in very young children. In some of the children of school age I believe there has been as high as a 20% absence from school during epidemics. I believe by vaccinating children you may cut down in the older population tremendously the amount of influenza that occurs, because it is true that the child does introduce a great deal of these infections into the home.

I want to thank Dr. Weller for his kind comments.

Isolation of Cytopathogenic Agents from Tracheal Secretions of Cases of Acute Laryngotracheobronchitis. A. J. BEALE,* D. MCLEOD,* W. STACKIW,* and A. J. RHODES, Toronto.

Acute laryngotracheobronchitis or "croup" is a prevalent disease in North America, now ranking fourth as a cause of admission to The Hospital for Sick Children, Toronto. Although a serious disease, modern methods of treatment have greatly reduced the mortality. The etiology still remains obscure, however, but there is some indirect evidence, put forward by Rabe (*Pediat.* 2:255 & 415, 1948) for example, suggesting a viral etiology.

Most patients are 1 or 2 years old, and the disease is rare in children over 5. There is nearly a 3:1 preponderance of males. The condition occurs mainly in the winter months, although a few cases do occur in the summer.

Investigations into the etiology have been made in Toronto since 1952, paying particular attention to the possibility that the condition is due to a virus. Bacteriological studies have been generally unrewarding as reviewed for example by Neffson ("Acute Laryngotracheobronchitis," New York, Grune & Stratton, Inc., 1949) in 1949. We found, in the winter of 1953-1954 that 23 of 70 patients yielded no pathogens. The commonest organisms isolated were Staphylococcus pyogenes and Streptococcus pneumoniae. Hemophilus influenzae Type

B was isolated from one patient, and no isolations of the diphtheria bacillus were made.

The early virus studies carried out in 1952 using mice and chick embryos which were negative were reported to this Society three years ago. In 1953 and 1954 tissue cultures of human embryo lung and monkey kidney monolayers became available and were used to study material from 21 cases. Tracheal secretions from two cases requiring tracheotomy yielded agents cytopathogenic for both types of culture. These agents were carried through five transfers in monkey kidney cultures. Material from three additional patients caused similar changes, consisting of clumping of the nuclei of cells and subsequent degeneration of the cell sheet into islands with vacuolation of the cytoplasm. At that time it seemed probable that these agents would fall into the then newly described APC group of viruses.

Encouraged by these findings, we inoculated material from patients seen last winter into newer types of tissue culture, namely, HeLa and trypsinized human amnion cells which appear free from "spontaneous" viruses found in some monkey-kidney cultures.

The results of virus isolation tests are shown in the table. At the top, the result for seven severe

Laryngotracheobronchitis, Hospital for Sick Children Toronto, 1955, Virus Isolation

Code Number of Patient	Virus Isolation	
	HeLa Cells	Human Amnion Cells
Tracheal secretion		
9	+	Not tested
1, 3, 4, 10	+	+
2, 5	−	−
Nasopharyngeal secretion		
6, 13	+	+
7, 11, 15	−	+
8, 12, 14	−	−

patients needing tracheotomy are shown. One patient, number 9, could only be tested in HeLa cells, but the agent also destroys amnion cells. Four agents were isolated in both types of cell and two cases were negative. The bottom half of the table refers to eight milder cases and posterior nasopharyngeal secretions were used as inoculum. Two patients yielded agents in both cell types, while three agents were only recovered in human amnion cells, suggesting these cells are more sensitive. Thus, a total of 10 viruses were isolated from the 15 patients.

Normal human amnion grown on coverslips and stained with hematoxylin and eosin consists of uniform cells with a clearly defined nucleus and cytoplasm. The normal cells show a nucleus with one or more nucleoli and surrounding cytoplasm. The infected cultures show loss of cells and clumping of the nuclei which are embedded in a syncytial mass of cytoplasm. No intranuclear inclusions have been observed.

These agents are transmissible in series and produce their effects more quickly on passage. Fifteen or more days may be required for initial isolation in HeLa cells, but on passage in human amnion cells cytopathogenicity is observed in seven or eight days.

It has not been possible to identify these agents. Four common respiratory viruses have to be considered. Influenza is probably excluded because of the failure to isolate a virus in eggs and because we have observed no hemagglutination of human Group O red blood cells at room temperature. APC virus is unlikely because the eight patients who were tested did not develop complement-fixing antibodies to APC virus during convalescence. Also the morphological changes in human amnion are unlike those seen with APC-3, for example. Herpes simplex is excluded on morphological grounds and because of the lack of pathogenicity to suckling mice. The changes are, on the other hand, somewhat similar to those described by Enders and Peebles (*Proc. Soc. Exper. Biol. & Med.* 86:277, 1954) for measles virus. However, we have not seen any nuclear inclusions such as are described in this infection. Also none of our patients developed a measles rash so were not in the prodromal stage of this disease when they had croup.

At present serum neutralization tests have been performed on four patients, and all four showed a rise in neutralizing antibody titer during convalescence, suggesting current infection.

The results described are typical of many observations now being brought forward when tissue-culture methods are applied to the study of diseases of obscure etiology. Some time must elapse before the pathogenic role of these agents can be established. Although agents have been isolated not only from the posterior nasopharynx but also from the tracheal secretions of a high proportion of cases, and the development of antibodies during convalescence has been demonstrated, no studies have been carried out on the prevalence of these agents in the respiratory tracts of normal children for example. The investigations of these agents are only at an early stage.

DISCUSSION

DR. HORACE L. HODES, New York: I'd like to ask Dr. Beale the range of the titer rise which he mentioned. Of what order of magnitude was this?

DR. SHEPARD, Seattle: I'd like to ask whether these were male or female amnion cells. I wonder if that would make a difference in your recovery of virus, because there is a sex difference in the disease.

DR. EDWARD F. RABE, Danville, Pa.: I was very pleased to hear this "beginning of the road." Some years ago we commented that acute infectious croup was due to a viral agent, but this was made on the basis of inference. Before that time and since then there have been hypotheses outlined concerning whether or not this disease was due to staphylococci, streptococci, or other bacterial agents. Personally, I felt that a large bulk of these cases has been due to a nonbacterial agent. I am pleased to see that at least one good possible suspect has been found.

One facet of the investigation which interested me was the fact that the etiological agent or the supposed etiological agent has been obtained in some instances from both the trachea and the nasopharynx. Earlier workers interested in the bacteriology of the nasopharynx and trachea in patients with croup have implied that the etiological agent must be sought in the trachea. Our work showed that the bacterial flora of the nasopharynx was a mirror of the bacterial flora of the diseased larynx and trachea. Certainly the nasopharynx is the easiest site to culture. I was, therefore, wondering whether or not the nasopharynx was as good a mirror of cytopathogenic agents found in the diseased larynx as it was for bacteria on the basis of consistent findings in a larger number of cases than those reported here.

DR. ALFRED FLORMAN, Manhasset, N. Y.: I'd like to ask the authors whether they have tested this agent for susceptibility to the usual chemotherapeutic agents.

DR. EICHENWALD, New York: I'd like to ask whether other tissues have been used in an attempt to isolate other agents from the trachea of cases of laryngotracheobronchitis.

We have also used the human amnion and, to a limited extent, have used fetal tracheal tissue. Apparently the fetal tracheal tissue will support agents which will not normally propagate in amnion cells, and therefore perhaps a different group of viruses can be isolated using a different tissue.

We have been able to isolate APC Type 3 from a number of patients with acute laryngotracheobronchitis and also from their contacts. However, the usual difficulty of establishing an etiologic role in the disease process for these agents arises and therefore at the present time we can only speculate about the role of this particular agent in acute laryngotracheobronchitis.

DR. ARDEN MILLER, Kansas City, Kans.: Do the authors have any information about whether or not these agents are immunologically related to each other?

DR. A. J. BEALE: First the question of titers. The neutralizing antibody titers have been in the range of 1:2 in the acute sera and 1:64 to 1:256 in the convalescent sera.

Chemotherapeutic agents, at least penicillin and streptomycin incorporated in the tissue-culture media do not have any inhibitory effect.

Earlier we tried to isolate agents in human fetal lung and trachea. Similar degenerative changes as described here were seen in some of these cultures inoculated with tracheal secretions.

We have not carried out any studies of the immunological relationships of the agents isolated, but they produce very similar changes in human amnion cells.

Cytopathogenic Enteric Viruses Associated with Undifferentiated Diarrheal Syndromes of Early Childhood. M. RAMOS-ALVAREZ,* Cincinnati. (Introduced by Albert B. Sabin)

The purpose of this study was to determine the incidence of infection with enteric viruses among infants and children who present themselves with the syndrome of gastroenteritis during the summer months. Rectal swabs and acute and convalescent phase sera were obtained from children who visited the clinics or were admitted to Cincinnati hospitals during the summer of 1955. Thus far the rectal swabs have been tested only in cynomolgus monkey-kidney tissue cultures and 24 cytopathogenic agents were recovered from 56 children ranging in age from a few days to 4 years. Fifteen of the agents were recovered from 38 children under one year of age (39% positive) and nine agents were derived from 18 children, 1 to 4 years of age (50% positive).

Serologic identification of the 24 cytopathogenic agents yielded the following results: 3 were type 1 poliovirus, 3 belonged to the Coxsackie family (one A 9 and two B 2), 2 belonged to the group of 13 new ECHO (enteric cytopathogenic human orphan) viruses (one type 2 and one type 8), and 16 strains could not be classified with any of the available pools of antisera for known cytopathogenic viruses of the poliomyelitis, Coxsackie, and ECHO groups. The behavior of these 16 unidentified agents in tissue culture suggests that they may belong to at least several different categories.

The high incidence of 43% virus recovery from children with gastroenteritis by the single technique of isolation in monkey-kidney cultures may be compared with an incidence of about 6% among 154 children aged 1 to 4 years who visited Cincinnati clinics for causes other than gastroenteritis during the summer of 1953. It is not improbable that the rectal swabs which yielded negative results in monkey-kidney tissue cultures may yield additional "enteric" viruses by inoculation of suckling mice and tissue cultures containing other cells such as HeLa or human amniotic cells. It is furthermore noteworthy that bacteriologic studies on 36 of these 56 patients yielded pathogenic bacteria (Shigella or Salmonella) in only 4 pa-

tients, 3 of whom also yielded cytopathogenic agents.

The high incidence of viruses of various kinds that were found to be associated with gastroenteritis in young children points to the fact that only simultaneous studies on children of similar age with and without gastroenteritis will establish the presence or absence of an etiologic association between the numerous viruses which may infect the human enteric tract and the undifferentiated syndrome of gastroenteritis.

DISCUSSION

DR. HODES, New York: I was very interested in Dr. Ramos-Alverez's paper, and I believe his last remark about the necessity for comparing the incidence of children without diarrhea is very important.

We have some data along this line confined to newborn infants. Over a period of two years we have examined the infants born in our newborn nurseries and have found a quite striking absence of the agents which have been referred to here today. On the other hand, in two isolated outbreaks of diarrhea in the nursery a cytopathogenic agent was recovered from one of these and in the other what appeared to be a Coxsackie-like virus. We had in this instance what Dr. Ramos-Alvarez asked for, an absence from agents in normal infants and on two occasions of infants that were ill with diarrhea—the viruses that I have mentioned.

There is one other thought that I have, and that is that diarrhea may be a nonspecific symptom, and one can't be sure that the presence of the virus in the stool is necessarily etiologic. I believe all of us are aware of the danger of the finding of the virus, plus even a titer rise, as establishing the etiological significance.

DR. STEIGMAN, Louisville, Ky.: I'd like to congratulate Dr. Ramos-Alvarez for an excellent report, and for emphasizing the recovery of multiple kinds of agents, despite common time, place, and common clinical syndromes, and for underscoring the thought that there may not be an etiological relationship in his cases.

This is in contrast with the earlier papers dealing with a single syndrome, in both of which the epidemics were studied in a single time and place; hence, one might expect to recover a single agent.

It might be appropriate to give a progress report on a paper submitted here nine years ago, in the pre-tissue-culture days, an epidemic of summer sore throat and grippe. Again, the epidemic was single with respect to time and place—it took place in Cincinnati, and it occupied a time span of about six weeks, and the clinicians and epidemiologists concerned were certain that a homogenous event was being dealt with. Fortunately, I have kept the material since then, and with the newer techniques, it has turned into a Pandora's Box of viruses; we have found Coxsackie A and B, ECHO of various numbers, and some that have not yet been categorized at all. It would be important in attempting to establish relationships between clinical syndromes and new agents to hold onto frozen specimens, and see what will evolve from their subsequent study.

DR. M. RAMOS-ALVAREZ: Well, I believe we are not trying to startle anybody with these data. We have just pointed out that, at least in this study of 56 cases, we have a very high incidence of associated virus infections and certainly that we cannot talk about just one agent as being responsible for the syndrome, but rather we have to talk about a great variety of them. The exact relationship of each one with the disease is a matter for future study.

Steatorrhea Related to a Factor in Cow's Milk.

MURRAY DAVIDSON * and RICHARD BURNSTINE,*
Cornell. (Introduced by Irving Schulman)

Despite many reports of milk allergy in children and some describing gastrointestinal disturbances and "sprue-life" pictures, there are no available studies which characterize the stools chemically or in which a systematic attempt has been made to isolate those factors in milk that might be responsible for these symptoms.

A 3-month-old child exhibited diarrhea from birth when fed cow's milk. The diarrhea responded to a soybean preparation. Studies of pancreatic enzymes, bacterial examination of stools, and studies of other factors which might have contributed to the picture were all normal. It was shown that the diarrhea was a steatorrhea in which both saturated and unsaturated fatty-acid fractions rose with ingestion of the offending agent. During these periods weight gain ceased. Nitrogen excretion was within normal limits.

By feeding the soybean milk preparation as a baseline nutrient and supplementing it with various additives during the observation periods, it could be shown that the diarrhea was precipitated by a commercial casein preparation and by a hydrolysate prepared from this material but that a highly purified casein preparation did not produce the steatorrhea. This suggested that the difficulty was related to some portion of the whey-protein fraction. Addition of one-third the normal intake of powdered whey proteins to the diet produced steatorrhea. The two major constituents of whey proteins which have been crystallized are alpha-lactalbumin and beta-lactoglobin. Each of these was fed to the patient in much smaller amounts than their normal content in whey. No steatorrhea resulted after feeding alpha-lactalbumin, but following the feeding of beta-lactoglobin in 1/100 the normal amount in one quart of whole milk there was a considerable degree of steatorrhea.

DISCUSSION

DR. DOUGLAS E. JOHNSTONE, Rochester, N. Y.: I believe this paper is a significant contribution to our knowledge of celiac disease. One of the things, it seems to me, that Dr. Davidson is saying is that allergies or allergens can be one more cause of the celiac syndrome.

Three years ago, to this Society, I had a paper read by title wherein we described the defect in vitamin A-ester absorption, compared with that of the alcohol in this condition, due, presumably, to allergic processes, and we have found more children showing this defect since then.

Dr. Davidson has bypassed one of our problems, namely, the question of whether celiac disease under any circumstances can be due to an allergic process, and has shown that that can be so, and apparently that a given protein can do it.

However, I believe many of us think perhaps the so-called "gluten celiac syndrome" may be an allergic process, and others feel that there is some other obscure biochemical process, and I wonder what other data there is to show that this is an allergic individual than the screen test—in other words, whether he had other allergic symptoms.

DR. GIULIO BARBERO, Philadelphia: I believe Dr. Davidson's case study raises a number of profound questions as to the mechanism of steatorrhea in this patient.

We have been interested in trying an unsplit milk antigen on the surface of the mucosa of the colon via a proctoscope. In a number of babies who have had milk allergy, i.e., diarrhea on cow's milk, responding to a vegetable protein such as sobee, one can produce an area of mild edema which suggests an urticarial-like process. This may be the gross appearance of the response of the bowel as a shock organ for some antigenic material.

In a later paper presented by title in this meeting, we have discussed the study of duodenal motilities in normal children. Such a technique might be of value to evaluate any motility disturbance produced by an instilled offending agent such as described by Dr. Davidson. X-rays in these babies by the usual barium method first and subsequently with the offending agent added to the barium may also demonstrate whether any motility disturbance is present.

DR. HAROLD E. HARRISON, Baltimore: I'd just like to have one point clarified.

I noticed in the whole milk studies that the coefficient of fat absorption was zero. How often, Dr. Davidson, have you found that the fat excreted was equal to the fat ingested? This seems to be a rather unusual degree of disturbance of fat absorption.

DR. SIDNEY Q. COHLAN, New York: In the last year and a half, we have had a rather unusual experience in the therapy of a large number of children who had been previously diagnosed as "celiac syndrome" and whom we characterize as "chronic non-specific" diarrhea.

Specific food sensitivity was incriminated in many of the cases. Following an accidental observation of it's efficacy, we have used diiodo-hydroxyquinoline in the treatment of 110 children presenting with chronic non-specific diarrhea. A double blind placebo study was included in our investigation. Marked improvement in stools with tolerance of a full diet while on therapy was observed in 65% of the cases treated.

DR. BESSMAN, Baltimore: I'd like to know if you have measured the glutamine, or apparent glutamine, of the blood of this patient, in the light of the findings of the Dutch workers with celiac disease.

DR. WILLIAM C. DEAMER, San Francisco: I'd like to ask Dr. Davidson if he has any other evidence that nutramigen contains unaltered milk protein, inasmuch as it is hydrolyzed and theoretically should not contain enough native protein to bring about such effects.

I noticed that there were several 24-hour test periods for the other substances tested, but only one for nutramigen. I wonder if he has any other evidence than this single 24-hour collection that steatorrhea resulted from the use of nutramigen, and also whether he did skin tests with nutramigen which indicated sensitivity.

DR. SAMUEL SPECTOR, Cleveland: I should like to question the use of the term "celiac disease" to characterize the clinical picture of the patient presented. The term, so stated, tends to imply, at least to me, that it is an entity with a fixed pathogenesis and an etiology which is allergy. As was so ably demonstrated by the authors, a specific allergen can certainly produce steatorrhea. In that situation as well as in inflammation, it would seem that the local reaction of the intestinal mucosa and alteration in motility could account for the interference in fat absorption. However, there is increasing evidence to suggest that the celiac state may be the result of an enzymatic block of an active transport machanism responsible for fat absorption. Until such time as the pathogenesis is known, it may be best to refer to the disorder as celiac syndrome and consider that the etiology may be multiple.

I should like to reemphasize the point made by the authors, as well as by other workers in the field in the past, that fat content can be increased in a stool which appears grossly normal. It has been interesting to us in performing fat absorption studies using I^{131}-labeled fat to find, not uncommonly, patients with poor nutrition and normal-appearing stools who have significant steatorrhea. Also, patients with steatorrhea who develop diarrhea can decrease absorption of fat to as low as 10%.

DR. HOLT, New York: I should like to congratulate Dr. Davidson on a beautiful piece of work. I believe it might also be worth while to point out that the idea that allergy plays a role in celiac disease goes back a long way.

I believe that Oscar Schloss obtained the first evidence for this, but certainly there could be no clearer demonstration than the one Dr. Davidson has given us. It is a relief to find that wheat gluten is not responsible for all cases.

DR. MURRAY DAVIDSON: I should like first to thank all the discussants for their stimulating comments. I hope, as somebody said yesterday, that I don't present another paper in trying to answer them all.

Perhaps we can group some of these. We have tried very studiously and assiduously in the preparation of this paper to avoid commenting on whether we thought that the basis for production of steatorrhea here was allergy to the specific protein, or perhaps some biochemical defect, and I believe some of the questions have touched on this problem.

Dr. Deamer's question about hydrolysis has bothered us also. We are interested in studying this patient further with various denatured and hydrolyzed preparations. Perhaps this phenomenon is not specifically related to the lactoglobulin, but to some constituent of the lactoglobulin and the mechanism is a chemical one. I don't believe we have enough data to do more than merely mention this now and not speculate further.

I thank Dr. Johnstone for crediting us with showing this first, but I feel the credit should belong to the Dutch and British workers who were the first to show the relationship of a specific protein to steatorrhea.

In our patient, we did not find eosinophiles in the stool. If I may for one moment make an aside, I believe it's possible that the locus of action of various diseases in the long gastrointestinal tract may vary all the way from the top of the esophagus to the lower colon. Mucus in the stool suggests that the patient has a disease in the lower portions of the bowel. Since there was no mucus in these stools, I wouldn't expect that we could find any of the eosinophiles, which are supposedly related to large-bowel allergy.

A further answer to Dr. Johnstone is that, while the child has been doing extremely well after his hospitalization and has gained relatively enormous amounts of weight, this child did have two attacks of asthmatic bronchitis, one at 4 and one at 5 months.

Dr. Barbero's questions are quite stimulating. We also gave this patient milk and lactoglobulin through a proctoscope. The bowel did become reddened when we introduced the material. Unfortunately on motility study, after not showing any reaction to two small introductions of saline and showing propulsive action with intracolonic introduction of 5 cc. of milk, he also displayed a marked propulsive activity with the repeat saline controls, and we therefore didn't present this data here because of the inconsistencies.

I think, however, Dr. Barbero's studies in the duodenum might prove very interesting, since the locus of action here is probably in the small bowel, and if he can demonstrate any change in the motility, this indeed would be quite important.

In response to Dr. Cohlan's comments, I was very pleased to have him get up. We also have a number of such patients as he has described. We have not treated them just as he does, but we are certain that these patients are not celiac disease, or syndrome, whichever one prefers of the terms. These patients do not have the highly specific type of diarrhea we have presented here but rather display a nonspecific diarrhea, probably large bowel in origin.

I should especially like to thank Dr. Holt for his kind comments, and in answer to Dr. Spector, we don't believe that the answer lies only in gluten and in lactoglobulin. Probably there are a number of other proteins involved, and in these patients elimination diets and careful controlled studies with various additives might prove the answer to isolating other factors.

We were just lucky enough to be dealing with a young infant in whom too many foods had not been introduced, so that the answer came our way easily.

Observations of a Biochemical Lesion in Allergy. JOHN D. CRAWFORD, GERALD A. KERRIGAN,* and MARY L. BERTUCIO,* Harvard.

Metabolic balance studies have been conducted in two infants shown to be allergic to cows' milk by passive transfer skin tests and repeated demonstration of reaction to exposure. The exposure reaction was characterized by evidence of peripheral circulatory failure including cyanosis, hypotension, elevated hemoglobin concentration, azotemia, hyperphosphatemia, acidosis, and hyperkalemia. Simultaneously, weight losses were small, only slight negative external sodium balance occurred but markedly positive balances of potassium and chloride were recorded. Using calculations based on external chloride balance and serum chloride concentrations to yield an index of extracellular fluid volume changes, the following internal shifts of water and electrolyte appeared to take place concomitantly with the development of hypovolemia: (a) expansion of extracellular fluid by amounts approximating 20% of the assumed normal starting value; (b) transfer of water from the intracellular to the extracellular compartment and to the excreta in amounts equal to approximately 40% of the intracellular fluid volume at the start of the expos-

ure reaction; (c) intracellular deposition of potassium in amounts equivalent to approximately 25% of the initial total body potassium as measured by radioisotope exchange, and (d) enrichment of the expanding extracellular fluid volume by sodium apparently derived largely from intracellular rather than from skeletal stores.

The development of the metabolic disturbance was uninfluenced by large doses of desoxycorticosterone; it was modified but not prevented by large doses of cortisone. In one infant the biochemical lesion was shown to be suppressed by administration of sodium lactate in company with the antigen. The observations will be illustrated and discussed with reference to available published data on the metabolic changes in hypersensitivity.

DISCUSSION

Dr. Robert E. Cooke, New Haven, Conn.: I believe this paper has been of considerable interest. We were fortunate enough several years ago to have studied a few of these children but without the great care that Dr. Crawford has demonstrated in his studies.

The children that we observed—and one of them was reported by Dr. Daniel Darrow in one of his papers on the treatment of diarrhea—in contrast to the milk allergies described by Dr. Crawford, had extreme losses in body weight on exposure to milk. These patients lost as much as 20% of the body weight in a period of 12 hours with large losses of extracellular fluid at the same time. These losses were subsequently accompanied by a very marked lowering of the serum potassium concentration, and they exhibited a picture quite different from the patients described by Dr. Crawford.

It seems to me that the findings of Dr. Crawford can be explained possibly by tremendous changes in the volume of fluid which is contained in the gastrointestinal tract, whether intraluminally or within the walls of this organ which has such a large surface area. I believe this situation may be analogous to a burn, that is, a massive insult to an organ with a very large surface area. Such an injury would lead to an outpouring of a large amount of fluid which would lead to a diminution in the circulating plasma volume in the presence of a large extracellular or transcellular volume. At the same time potassium might accumulate in the extracelluar space and possibly shifts of sodium and hydrogen or potassium might occur across the cells as he described.

Dr. Frederick C. Moll, Seattle: Some years ago, Dr. Unger demonstrated in the test tube that with an allergic reaction there was a release of a proteolytic enzyme.

Recently we have been able to purify to some degree the naturally occurring serum proteolytic enzyme inhibitor. In contrast to the enzyme, it is quite sensitive to change in pH, and I should like to ask Dr. Crawford if he has any direct or indirect evidence of the proteolytic activity of the serum of his patients.

Dr. William McLean Wallace, Cleveland: I was interested to note that Dr. Crawford's data show that as extracellular fluid gains water and sodium from the intracellular volume the amount of exchangeable potassium goes up. Does this mean that potassium is becoming exchangeable or is it coming from outside of the body?

Dr. Charles U. Lowe, Buffalo, N. Y.: I believe Dr. Crawford's paper is extremely interesting to all of us who have been interested in the problems of intestinal insufficiency. My purpose in commenting is to raise some question about the acceptability of allergy as the chief or the sole explanation for the phenomenon that these patients exhibited.

Now, I base my question upon observations which Dr. May and I were able to make about six years ago on several patients with apparent intolerance to complex carbohydrates. At least, that was the title which we gave to the syndrome.

Now, as you know, this syndrome apparently no longer exists, thanks to the work of the Dutch investigators. It is clear that those patients who were thought to have intolerance to complex carbohydrates are really apparently sensitive to glutamine, and if the amine group is removed from glutamine, even as it is contained in gluten, apparently these patients no longer exhibit intolerance, and furthermore they exhibit certain specific abnormalities of intestinal absorption to the glutamine. All of this work, in other words, suggests a biochemical lesion.

Now, the patients whom we studied had clear-cut intolerance to complex carbohydrates, and exhibited it by marked steatorrhea every time starch—in this instance, actually, starch which contained gluten—was added to their diet. But as I read Dr. Crawford's conclusion in his abstract, and listened to his paper, he presented the same observations which we had made on our patients.

Now if patients who have a biochemical lesion which is exacerbated by gluten, or manifests itself by increased absorption of glutamine from the intestinal tract, undergo the biochemical changes of the shift in sodium and increased potassium, I wonder if one would not be justified in questioning the interpretation that Dr. Crawford has presented—and my comments in no way disparage his observations. I'm simply questioning his conclusion of allergy.

I have one other point. In the previous paper, the Dutch investigators were credited with indicating that the per cent fat absorption was the correct diagnostic criterion of steatorrhea. However, I

believe these findings were anticipated by Dr. Holt and the English investigators.

Dr. Milton R. Rapoport, Philadelphia: The description of the magnitude and gravity of the disturbance of water and electrolyte status accompanying the allergic reaction in Dr. Crawford's patients are impressive and important observations. These data are valuable additions to the already existing body of fact which relates the allergic reaction and changes in salt and water content of the body. Both clinically and experimentally it has been shown that the intensity of the reaction following antibody-antigen union in vivo may vary quantitatively with the state of hydration of the organism. Eczema and asthma may become mild or temporarily disappear in a dehydrated child. Similarly, preliminary dehydration of passively sensitized guinea pigs may ameliorate or prevent completely the appearance of the anaphylactic response following the injection of specific antigen. Conversely, Dr. McQuarrie showed that water loading induced by vasopressin (Pitressin) tannate could aggravate asthma in children. The same effect is seen in over-hydrated sensitized pigs.

The only small objection I wish to raise is that these well-timed careful observations do not describe a biochemical lesion, in the sense in which I understand a specific biochemical lesion.

These are descriptions of phenomena, perhaps of a failure in homeostasis—a biochemical lesion at the molecular level is not evident in these observations. Actually, my objection is based on semantic grounds. The title of the paper misled me last night—and I feel it is a misnomer for this interesting presentation—the biochemical defect of allergy is something else again.

Dr. Hodes, New York: Dr. Gellis is startled to have me get up, and I suppose I don't qualify as a chemist at all, but I should like to say that the first slide which Dr. Crawford showed was very similar, as I remember, to the data found by Cachey and Sweet in our laboratory on children who were suffering from diarrhea due, presumably—certainly—not to allergy, but to infection.

Those children suffered a loss of extra- and intracellular water, but under treatment they had a great rise in extracellular water, with continued diminution in intracellular water.

I should like to suggest that this is not necessarily connected with allergy, but may be associated with diarrhea of any cause.

Dr. John D. Crawford: I want to thank Dr. Cooke for his suggestion that this large amount of extra extracellular fluid might be contained in the gut wall. I will remind him, however, that the second infant at no time had any real diarrhea.

Dr. Moll, I am afraid we did no test of proteolytic enzyme activity in the serum of either of these children.

In answer to Dr. Wallace's question, the potassium gain which occurred during metabolic deterioration was obtained from sources outside the body. I would presume that in 2-month-old children such as these our exchangeable potassium measurements were quite reliable indices of total body potassium. Perhaps Dr. Forbes can help us on that later on.

We now come to a group of questions as to whether or not this was allergy. I don't have, as Dr. Davidson had for celiac disease, a definition of "allergy." I wish I had. But I'm sure if it were adequate, it could not be contained in as brief a statement as his for "celiac disease."

In several respects these children were classical allergy patients.

The first of the two patients described is an only child. His mother is a severe asthmatic. After several episodes of gastrointestinal reaction to milk feeding as an infant he has gone on to develop eczema and asthmatic bronchitis. He continues highly sensitive to cow's milk. A number of accidental exposures in the home as well as three intentional challenges under hospital auspices have made him quite ill.

The second patient has a most interesting family tree from the allergic viewpoint. Both parents and many aunts, uncles, and cousins show one or several allergic manifestations such as hay-fever, eczema, hives, asthma, and the like. This patient, too, has gone on to manifest mild eczema.

Protein Electrolyte Interactions: The Possible Binding of Small Ions by Human Serum Proteins. Ralph J. Wedgwood, Melvin D. Schoenberg,* and William B. Weil,* Western Reserve, Cleveland.

Protein gradients can be established in protein-containing solutions by ultracentrifugation. Such gradients allow the determination of relationships between the protein and electrolyte concentration in the solution and have been used in the past to determine the protein binding of calcium.

Gradients were established by this manner in normal human serum. Aliquots at various levels in the gradient were analysed by standard methods for sodium, potassium, chloride, calcium, and protein concentration. The data obtained were converted to concentration per unit mass of serum water and regression equations computed for the relationship between protein and electrolyte concentrations.

The data obtained indicate that with increasing protein concentration there is also an increase in the concentration of sodium, potassium, calcium, and chloride. The changes for cation excede that expected from the Donnan equilibrium and, therefore, could not be explained on this basis. The change in chloride concentration was in a direction opposite to that expected from the Donnan effect.

The regression line for the relationship between calcium and protein concentration agrees entirely with that expected from the known binding of calcium by serum protein. The data for sodium, potassium, and chloride are not inconsistent with a hypothesis that these ions are also protein-bound to some extent. The data suggest that the type of binding, however, would be of a different nature.

Making the assumption that the concentration changes were due to protein binding, a "true" serum water concentration of electrolyte was calculated. The difference between the electrolyte concentration in the calculated serum water and whole serum was approximately 1.8 mEq/L. calcium, 7.8 mEq/L. sodium, 0.3 mEq/L. potassium, and 11.9 mEq/L. chloride. The sum of electrolyte supposedly "bound" approaches 23 mEq/L. Since the sum of the cation approximates the anion, electrical equivalence is unaltered and the charge on the protein unchanged. If these 23 mEq/L. are indeed osmotically inactive, the osmolarity of serum would be less than the usual 310 mOsm/L. assigned to it and closer to 290 mOsm/L., a figure which is, according to recent reports, more close to the value obtained by actual measurement.

DISCUSSION

Dr. Robert E. Cooke, New Haven, Conn.: I should like to ask the authors how they reconcile these data with the observations made by others on fluids which have been obtained as ultrafiltrates in vivo. Such analyses show little evidence of binding of sodium, potassium, and chloride.

This same question would apply to the studies on ultrafiltrates obtained from units such as the Lavieties ultrafiltration units. I am sure that there was no difference of 15 mEq. of sodium between the two sides of such a unit when expressed per kilogram of water.

The other question I should like to ask is whether or not pH changes have been observed in the various layers since the calculation of the Donnan distribution depends a good deal on these. Finally, there is some question as to whether or not activity coefficients should be used in the calculations rather than concentrations, since in the layers with high protein concentration the amount of water becomes very, very low.

Dr. Jack Metcoff, Boston: I think Dr. Wedgwood's report is an important one, because it does bring to the fore the use of serum measurements as a basis for estimation of concentrations in extracellular fluid.

For many years, of course, these have been corrected both by application of Donnan equilibrium factors, as well as corrections for actual measurement of water.

I wonder about one thing, that is if Dr. Wedgwood had analyzed different sections in the tube, because of the fact that while the tube is in the ultracentrifuge one would not expect to spin small molecules out of the tube under such a gravitational field, one still might get gradients of these molecules.

The second thing that is of some interest, as he mentioned, is that most laboratories that are measuring osmolarity in serum, either by freezing-point depression or by vapor-pressure techniques, are finding that the average normal value for freezing-point in depression for osmolarity amounts to something between 280 and 295 mOsm/L.

Dr. Bessman, Baltimore: I apologize for entering into this salt-and-water business, but it does have some interest from the standpoint of the question of which ions follow the protein. It seems to me that all the positive ions were parallel in their movement, and this would hardly agree with a specific finding of small particles.

Rather, it seems a relative, nonspecific one, and might follow along with a separation of charges, which happens with these large molecules.

The second point is the great scatter of the calcium data, with, it seemed to me, higher values in the higher concentrations of protein. Might this relate to the binding of calcium to a specific protein?

Dr. Ralph J. Wedgwood, I should like to thank everyone for their comments.

We are cognizant of the differences between our data and the data of others. Some of these differences we believe to be related to methodology. Ultracentrifugation is in many respects more gentle physicochemically than dialysis across membranes. In addition the small changes we have presented would only be seen by multiple determinations from several samples because of the large error of measurement.

Changes in pH need not necessarily have occurred in the protein gradients in the tube. The binding calculated did not result in any major disturbance of electrical equivalence. We did not, unfortunately, attempt to determine whether such pH changes did actually occur. We did attempt to find out whether the binding was pH dependent. We were able to demonstrate this to a certain degree for calcium but not for sodium, potassium, or chloride. Our inability to demonstrate pH dependence may have been a methodologic artifact rather than an actuality; there was a great deal of scatter in all the data, proportionately more apparent for calcium. Parenthetically, we could not attribute the scatter to the nature of the proteins in the gradients; we did not determine the identity of the proteins at the various levels. In our calculations we used standard "textbook" Donnan factors. The activity coefficients used in these factors are admittedly idealized, but variation in activities unless extreme would not alter the interpretation of these

data greatly. It is unfortunate that we could not measure activities directly.

Finally, with the force fields we used one would not spin down a small ion—such as sodium—alone. One cannot, at such speeds, spin the salt out of water. Such a micromolecule would only come down if it were closely associated with a macromolecule—such as protein. The degree of binding or the closeness of association might be tight or loose, but it is still, in essence, binding. I have no idea of the strength of any of the binding that we have suggested be present in serum. The binding or association for potassium and sodium would appear to be different from that shown previously for calcium and magnesium. We wonder whether the binding of sodium or potassium might involve a mutual sharing of the environment around both the protein and the electrolyte. Both protein and electrolyte have an environmental shell or milieu in which they exist and this milieu can be shared—for instance, by the sharing of charges or sharing of water. Such binding might be nonspecific as far as charge is concerned, yet quite specific in respect to the sharing of the surrounding shell of water.

Idiopathic Hyponatremia in an Infant with Diffuse Cerebral Damage. WALLACE W. MCCRORY and DUNCAN MACAULEY,* Pennsylvania.

The occurrence of hyponatremia in patients with acute or diffuse central nervous system disease has long been recognized, and the discovery that these patients continue to excrete considerable amounts of sodium and chloride in the urine in spite of low levels in the plasma has led to the concept of "cerebral salt-wasting states." The hyponatremia is generally resistant to correction by salt loading and the use of salt-retaining steroids, such as desoxycorticosterone (Doca) acetate.

We have observed an infant with diffuse cerebral damage, probably the result of birth trauma, in whom hyponatremia was discovered in the course of routine investigation. The duration of the condition is therefore unknown. The child was studied under conditions of varying salt and water intakes, and an attempt was made to determine the basic underlying mechanism of the hyponatremia.

Renal-function studies eliminated kidney disease as the primary cause of the disorder. Desoxycorticosterone acetate and fludrocortisone acetate had no appreciable effect on the hyponatremia. Very large salt loads given concurrently with large water loads failed to restore the serum electrolytes to normal. Large salt intakes with near normal water intake resulted in a rather unstable return to customary levels. The same fluid intake with a normal salt intake led to a precipitous fall in serum electrolyte levels. When the fluid intake was restricted with a normal salt intake, the serum sodium and chloride rose to the normal range. This observation was made on three separate occasions.

Total body chloride was estimated, using the thiocyanate space as a measure of the chloride pace on four occasions at widely different levels of serum chloride. The results showed no significant change in total body chloride which was within normal limits. Increases in thiocyanate correlated fairly well with increases in body weight. The hyponatremia consequently appears to result from dilution due to water retention rather than a salt-wasting state.

The infant demonstrated a diminished capacity to respond to an acute water load by a water diuresis. The subject did not achieve either as high a rate of urine flow or as low a urine solute concentration as was observed in normal infants similarly studied.

From these observations, it was concluded that the hyponatremia was possible due not to excessive losses of salt but to an inability to excrete water normally. Attempts were made to assay the level of antidiuretic activity in the plasma during a phase of hyponatremia, and evidence of enhanced activity compared to a normal infant was obtained. It is concluded that in this case there was a failure to respond normally to the stimulus of plasma dilution by a reduction in the output of antidiuretic hormone. This mechanism could explain the persistent hydremia observed in the subject when on normal fluid intakes.

Evidence in support of this hypothesis will be presented from other sources and the implications of this concept will be discussed.

DISCUSSION

DR. DONALD BROOK CHEEK, Cincinnati: We have been interested in recent years in the disturbance of water and electrolyte balance in tuberculous meningitis, and our data, published and unpublished, indicate, as in this case, that there is no loss of total body chloride. The total body water is normal, or increased in some instances. The total water may amount to 80% of the body weight, which is about what one would consider normal, if a child was completely devoid of fat.

Following along these lines and realizing that there may be some defect in water excretion, we have given three patients with tuberculous meningitis water loads of 3% to 5% of body weight. In each instance there was no difficulty in excretion of the water.

I feel, however, that some patients do show some difficulty in the excretion of water, since in one instance the weight was linearly related to the fluid intake.

I should like to point out that the children with tuberculous meningitis have a very low concentration level of serum sodium and chloride, which is always a temptation for some people to want to raise this level with hypertonic saline. I feel that,

since these patients often reveal a metabolic alkalosis, if anything, the total body sodium must be increased, and I therefore feel that the term "cerebral salt wasting" is somewhat inappropriate in tuberculous meningitis. One should bear in mind the results of the studies of Rappoport, West, and Brodsky, where they showed that children with tuberculous meningitis can neither clear nor conserve a salt load. The fact that they cannot clear a salt load is important.

Dr. Doxiadis, in England, gave these children high salt loads with fatal result in one patient.

Dr. William B. Weil, Cleveland: We are especially interested in this report because of a child we have followed for the last few years. She was first studied as an infant with diarrhea and hypertonic dehydration. Her serum sodium was 190 mEq/L. At that time she had an abnormal EEG which became normal in 10 days. Following the acute illness, her development was noted to be retarded. Her serum sodium remained at 155-160 mEq/L. There is no evidence of diabetes insipidus, but she has a decreased diuretic response to a water load, and her serum sodium can be lowered to 140 mEq/L. with such a procedure. However, when she is allowed water and food ad lib. the serum sodium returns to the higher level.

We have had the feeling that this child has a cerebral defect which includes some element of the osmoreceptor system. This could represent a response opposite to that which the Philadelphia group has reported.

Dr. Henry W. Baird, Philadelphia: I'd like to ask what electroencephalographic changes occurred during the observed period and what changes occurred in the convulsive pattern of the child during the observed period.

Dr. Harrison, Baltimore: As Cheek pointed out, this problem of hyponatremia is quite common in tuberculous meningitis, and Finberg and I, studying a series of cases, noted that muscle biopsies taken during a period of hyponatremia showed a rather interesting finding, namely, a high muscle sodium and low muscle potassium at the time that the serum sodium and chloride concentrations were reduced, and these patients, very frequently show a tendency to further depression of chloride when given fluids devoid of potassium—in other words, when given parenteral fluids over a long period of time.

Larragh has shown that parenteral administration of potassium may temporarily raise the serum sodium in certain hyponatremic patients, and I should like to ask Dr. McCrory and Dr. Macauley if they did any studies on serum-potassium concentrations in their patients.

I can't resist at least mentioning an unusual case, and Dr. Weil has already given me an opportunity.

Some years ago I had the opportunity to study a woman with diabetes, alcoholism, and serious nutritional deficiencies associated with alcoholism, with severe cerebral damage. She had a serum sodium of 105 mEq/L. without any of the evidences usually associated with low serum-sodium levels. She did not have adrenal insufficiency.

The serum sodium was not affected by injection of desoxycorticosterone acetate and could not be raised permanently by large doses of sodium. She had no evidences of hypovolemia.

As her alcoholism came under control in a hospital environment, her general condition improved. Her cerebral functions also improved, and concomitantly with that her serum sodium rose to normal.

There are some extremely interesting correlations between the central nervous system and serum sodium levels, but I think we are still quite undecided as to what are the primary mechanisms or through what mechanisms these effects are exerted.

Dr. Malcolm A. Holliday, Indianapolis: I think a specific lesion in the nervous system has been produced experimentally in animals leading to hyponatremia and another leading to hypernatremia; I wonder, however, if anyone has any data to demonstrate whether any of the patients with hyponatremia could tolerate a salt-free intake if water was restricted, or whether they were all a homogeneous group who had simply a defect in water metabolism.

Dr. Edna Sobel, Boston: The condition described surely resembles water intoxication with an increase in extracellular water and concomitant depression of sodium concentration. We know that this occurs in the presence of excess antidiuretic hormone and that patients with adrenal insufficiency have a limited capacity to excrete a water load and are especially susceptible to water intoxication. However, this disturbance in Addisonian patients can be corrected by carbohydrate-active adrenal steroids (cortisone, hydrocortisone, adrenal extract) rather than by sodium-retaining steroids (desoxycorticosterone acetate or fludrocortisone acetate in the usual therapeutic amounts). So, it seems to me that failure of the child described to respond to desoxycorticosterone acetate therapy does not cast light on the adrenal status, although I would not suggest that the patient might have adrenal insufficiency.

Experimental Studies of the Mechanisms Producing Hypocalcemia in Hypernatremic States. Laurence Finberg, Johns Hopkins.

Hypocalcemia is encountered frequently in infants with hypernatremic dehydration. Hyperphosphatemia or post-treatment dilution by an expanded extracellular fluid have been suggested as the important factors, but an analysis of clinical material indicated that other factors must also operate. Experiments were carried out to elucidate the mechanisms.

Young male thirsting rats were injected intraperitoneally with hypertonic solutions of sodium chloride and bicarbonate. The animals were bled and killed at subsequent intervals, and the serum and total carcass were separately analyzed. The serum determinations included Na, K, Cl, Ca, P, CO_2, urea N, H_2O, and total protein; the carcass analysis included Na, K, Cl, H_2O, fat, and total protein; the carcass analysis included Na, K, Cl, H_2O, fat, and total nitrogen. Urine was also collected for the experimental period and analyzed for electrolytes.

Hypocalcemia could be regularly produced in this manner 24-48 hours after injection. Comparison with thirsting control animals demonstrated that this effect was independent of serum phosphorus levels. Comparison with thirsting and nonthirsting uninjected animals demonstrated that the volume of the extracellular fluid (chloride space) was likewise not a factor. Increased calcium losses in the urine were insufficient to account for the reductions in serum concentrations. The hypocalcemia was more closely correlated with a rise in total body Na content than with increased serum Na concentrations. Under certain conditions the latter occurred without hypernatremia but with hypocalcemia.

The K/N ratio was found to be reduced when Na loading resulted in hypocalcemia. Moreover in all of the hypocalcemic animals the carcass Na/K ratio, which is usually less than one in control animals, became greater than one. Additional experiments showed that K-deficient animals did not develop hypocalcemia unless they were Na loaded and that Na-loaded rats did not become hypocalcemic if acute K deficiency was prevented by simultaneous K loading. Thus hypocalcemia resulted only if both Na excess and K deficiency were present, neither condition alone sufficing.

It is therefore concluded that experimental Na loading of rats produces Na excess and K deficiency which in turn are accompanied by hypocalcemia. The latter appears from a temporary alteration of the equilibrium between extracellular calcium and calcium stores.

DISCUSSION

Dr. Wallace, Cleveland: This is an interesting paper and bears on the problem of convulsive episodes occurring in infants recovering from hypernatremia. Many have noted the beneficial effects of calcium administration.

Balance studies during onset and recovery from hypernatremic states show no significant changes in potassium balance. The only significant changes have been in the balance of chloride. These have been rather spectacular. This suggests the possibility of very marked changes in intracellular acid-base balance or intracellular volume changes.

Of course, balances may be no good at all and ours as bad as others, but the problem still remains. I should like to ask if Dr. Finberg has any data on the volume of the body-fluid compartments.

Dr. Holliday, Indianapolis: I believe he mentioned that he did do serum bicarbonates, and there was a correlation between the serum bicarbonates and $P\text{-}CO_2$. Is that right?

Dr. Laurence Finberg: In answer to Dr. Wallace's question about infants, not all infants with hypernatremic dehydration, of course, show hypocalcemia. There may be a variety of ways of arriving at the hypernatremic state, and I'm not at all sure that what we have done in these animals correctly represents what occurs in the infants.

We did not do pH determinations of extracellular fluid. We did do bicarbonates on the serum. The bicarbonates were pretty much the same in the control animals as they were in the experimental animals.

I might add that though I didn't show it in data that were presented we did do some animals with sodium chloride load, and the same effect seemed to occur on the calcium.

President Zuelzer: I think it's time that we proceeded from water intoxication to some more potent chemical, and I will not take up any more of your time, except to say that it has been a great privilege to have been connected with this meeting.

I want to thank the speakers for the excellent presentations that they have given, and the discussants, and, above all, those who still spoke to me in the lobby even though they were not on the program.

The point that I want to make is that this Society has grown so large, and I think so healthy, that by far more papers have been submitted than could possibly be accommodated on the program. This has put not only those who were not represented under frustration, but also me under considerable nervous strain, and I did feel badly, because there were many excellent papers which would have made an equally good program. Even so, I felt that the meeting did illustrate the point I was trying to make yesterday as to how encyclopedic this Society has become. The fact that we started with rats and ended with rats was purely coincidental.

This will conclude the twenty-sixth Scientific Session.

Papers Read by Title

Association of a New Type of Cytopathogenic Virus with Infantile Croup. Robert M. Chanock,* Cincinnati. (Introduced by Albert B. Sabin)

Agents producing an unusual "sponge-like" cytopathogenic change in monkey kidney tissue culture were isolated from the pharyngeal swabs of 2 of

11 infants with croup. The infants from whom the agents were isolated and 3 additional patients developed a significant increase in neutralizing and/or hemagglutination-inhibition antibody during convalescence but failed to develop antibodies for the group specific RI-APC, CF antigen. The two agents isolated appear to be similar antigenically. Human amnion cultures also respond to infection with the production of a "spongy" cytopathogenic change and are 10 times more sensitive in detecting the "spongy" agent than are monkey kidney cultures. Infected monkey kidney tissue culture fluid agglutinates chick erythrocytes and in lower titer human "O" red cells. Hemagglutination of chick erythrocytes is rapidly reversed at room temperature or 37 C but differs from that produced by influenza, mumps, or Newcastle virus in lacking an eluting enzyme—resuspension of hemagglutinin-erythrocyte mixtures held at 37 C for two hours results in a restitution of the original positive agglutination patterns.

The agent, which is filterable, does not produce hemagglutinins after intra-amniotic or intra-allantoic inoculation of embryonated eggs. The agent lacks pathogenicity for suckling mice when inoculated intracerebrally and subcutaneously and for weanling mice by the intranasal, intracerebral, and intraperitoneal routes. Antigenically the "spongy" agent is unrelated to mumps, influenza A- A^1- B-C, Sendai, or Newcastle viruses. Hemagglutination-inhibition antibody is possessed by 30% of infants and young children (2½ months to 3 years) and 75% of young adult males.

The high incidence of "spongy" agent infection in croup patients suggests that this virus may be at least one of the etiological agents of this clinical syndrome, but extensive control studies will be necessary to establish a specific etiologic association.

An Evaluation of Cranial Percussion and Its Usefulness in Physical Diagnosis in Children. CHARLES KENNEDY,* PHILIP DANUFSKY,* ABRAHAM HAREL,* ROBERT K. JONES,* Pennsylvania. (Introduced by Robert Kaye)

Cranial percussion, used widely by a few clinicians both in the recognition and localization of intracranial pathology has had limited acceptance among pediatricians as a useful procedure in physical diagnosis. The tympanitic note found in advanced hydrocephalus, often equated with the cracked-pot sound is usually only of confirmatory diagnostic value, the gross appearance being sufficiently characteristic. In infants and children with increased intracranial pressure of short duration there is often considerable disagreement even among experienced examiners as to an alteration of the usual flat percussion note. Presumably this is due to the variation from individual to individual in the manner in which the technique is performed or to the fact that the sound elicited is modified so slightly from the "normal" that it is not possible for most examiners to discern the difference. Therefore a procedure was designed for objective comparison of sound waves produced by striking the head gently in the region of the pterion in the manner described by Macewen.

Using a contact microphone suitably amplified and a cathode ray oscilloscope transients were photographed with a 35 mm. camera. On comparing records obtained with a variety of percussion instruments of different texture (ivory, felt, rubber, and finger) only minor variations in the transients were observed, and therefore it was concluded that the transients reflected primarily the resonance characteristics of the cranium and its contents not significantly modified by those of the percussion instrument itself. The effects of increasing the intensity of the percussion blow were found to be (1) an increase in the amplitude and duration of the transients and (2) an increase in the percentage of high frequency waves (1500 c. p. s.) which are superimposed on a basic frequency in the range of 100-300 c. p. s. The latter was found to be true only in older children and adults.

A standardized procedure was adopted and records were made on normal infants and children of various ages. These are compared with those obtained in a variety of pathological conditions including hydrocephalus, subdural hematoma, intracranial tumors and Mediterranean anemia. Marked differences were observed in both frequency and attenuation of the transients with different ages and in a variety of pathological conditions.

Urinary-Tract Infections in Patients Severely Paralyzed Following Poliomyelitis. HARRIS D. RILEY JR.,* Vanderbilt. (Introduced by Amos Christie)

Urinary infections occur frequently in patients with severe paralysis following poliomyelitis, and are an important cause of morbidity and mortality. Despite the unfavorable influence of urinary infection on the general health of these patients, little information is available concerning the casual relationships in this situation. Although recumbency, repeated catheterization, renal and bladder lithiasis, extensive paralysis, and other abnormalities appear to predispose to urinary infection, the relative influence of these factors has not been studied or elucidated. Moreover, treatment has been far from satisfactory, especially in the more severe cases.

In the present report, the incidence, severity, and effect of antimicrobial therapy or urinary tract infection in 35 patients severely crippled with poliomyelitis were studied over a one year period. A satisfactory method of obtaining urine cultures in females without resort to bladder catheterization was devised and will be presented. By means of

a regular program of urine cultures and other procedures it was found that bacteriuria and pyuria commonly existed without apparent symptoms of urinary infection, and that clinical symptomatology varied greatly among patients without respect to the degree of occurrence of these signs. Thirty of the study group had definite and three had questionable urinary-tract infections at some time during the study. Thirteen patients developed urinary calculi which appeared to follow persistent urinary infection.

Among 624 cultures obtained, 82.6% yielded one or more of 12 different aerobic species of bacteria. Proteus bacilli and Aerobacter aerogenes constituted 74% of the bacterial species isolated. Rapid increase in drug resistance followed institution of treatment, which was followed by the rapid reappearance of drug-sensitive strains when therapy was stopped. In many instances the offending pathogen was eliminated from the urine by antibacterial therapy only to be replaced by another species, which often became rapidly resistant to all agents. An overgrowth of Gram-negative organisms in the respiratory tract was commonly observed as a consequence of antimicrobial therapy for urinary-tract infections.

Observations of changing resistance patterns in response to therapy suggest that more optimal regimens of treatment could be devised. The role of prophylaxis and other implications of the study will be presented.

Further Inquiry into the Pathogenesis of Hemophilus Influenzae. SARAH WOOD SELL,* Vanderbilt. (Introduced by Amos Christie)

Of the six known types of Hemophilus influenza, only type b has been well established as a pathogen. Previously, type a, as well as b, was implicated in bronchiolitis in infants. In the present study, cultures were obtained from children with various forms of respiratory disease. When a heavy growth of H. influenza (of any type) was found, acute and convalescent serum samples were collected and tested for significant rises in specific antibody titres.

Results were as follows:

Acute Bronchiolitis—9 patients
- Antibodies**: Type a = 3; b = 3; d = 2; e = 1
- Cultures: Type a = 2; b = 2; d = 1; Not typable = 4

Pneumonia (Without Empyema)—6 patients
- Antibodies**: Type a = 2; b = 3; c = 1
- Cultures: Type a = 2; b = 2; c = 1; Not typable = 1

Upper Respiratory Infection with Purulent Conjunctivitis—5 patients
- Antibodies**: Type a = 1; b = 3; d = 1
- Cultures: Type a = 1; b = 1; d = 1; Not typable = 2

Croup—3 patients
- Antibodies: Type b = 2; c = 1
- Cultures: Type b = 2; c = 1

Acute Pharyngitis—4 patients (all adults on the staff)
- Antibodies**: Type b = 1; c = 3
- Cultures: Type b = 1; c = 1; Not typable = 2

Purulent Otitis Media—2 patients
- Antibodies: Type a = 1; b = 1
- Cultures: Type a = 1; b = 1

Whooping Cough—1 patient
- Antibodies: Type a = 1
- Cultures: Type a = 1

Meningitis—5 patients
- Antibodies: Type b = 5
- Cultures: Type b = 5

Conclusions.—Significant rises of type-specific antibody titres were developed in patients with a variety of respiratory diseases from whom H. influenzae, types a, b, c, d, and e, were cultured. This suggests that all these types of H. influenzae may be virulent.

** A significant rise in convalescent serum in type-specific antibodies suggests that the infecting organism was originally type-specific even though we were not able to demonstrate it from our cultures.

Rates of Hemoglobin and Red Cell Synthesis and Destruction in Congenital Hemolytic Syndromes. IRVING SCHULMAN, MARION ERLANDSON,* ZINET CURRIMBHOY,* and CARL H. SMITH, Cornell.

Hemolytic states are characterized by abnormally rapid rates of red cell destruction. The severity of anemia in such a state depends upon the degree to which the marrow may compensate, by increased production, for the decreased longevity of the red cells. Establishment of equilibrium, with steady red cell and hemoglobin concentrations, represents

that point at which the daily amounts of red cells and hemoglobin being synthesized equal the amounts being destroyed. In such a steady state it is possible to calculate, by determining the red cell mass and the red cell life span, exact rates of production and destruction of red cells and hemoglobin.

Blood volume measurements and red cell survival studies, using radioactive sodium chromate, have been performed on 15 patients with four of the congenital hemolytic syndromes: Cooley's anemia (7), spherocytic anemia (4), sickle-cell anemia (3), and sickle-cell-thalassemia disease (1). Each patient was at equilibrium and, varying degrees of anemia were represented in the group. Mean red cell life-span averaged 9.0 days in sickle-cell anemia, 15.8 days in congenital spherocytosis and 20.1 days in Cooley's anemia. Rates of hematopoiesis close to six times normal were found to occur in sickle-cell anemia and congenital spherocytosis. In Cooley's anemia red cell synthesis averaged only 3.7 times normal, while hemoglobin synthesis averaged 3.0 times normal. Synthesis of fetal hemoglobin in Cooley's anemia, however, reached levels of 150 times the normal rate.

Although the above studies gave definitive data on red cell and hemoglobin exchange they did not explain entirely the hemoglobin and red cell concentrations maintained in the individual patients. Further studies disclosed modes of blood volume adjustment which appear specific for each of the diseases.

Finally, analysis of the data suggested certain fundamental physiologic facts related to the regulation of blood formation.

Dissociation of Urinary Concentrating and Diluting Ability in Potassium Deficiency. MALCOLM HOLLIDAY and WILLIAM SEGAR,* Indiana.

A renal tubular lesion has been described in association with potassium deficiency and alkalosis. Recently a defect in ability of the rat to concentrate urinary solute was demonstrated in this circumstance. The present study was designed to compare this concentrating defect in (a) potassium deficiency with alkalosis and (b) potassium deficiency without alkalosis. In addition, studies on the ability to dilute urine were made.

A basic diet deficient in sodium, potassium, chloride, and phosphate was fed all groups. The control group received a drinking solution containing these ions in appropriate concentrations. The second group received sodium bicarbonate solution to drink. The third group received distilled water.

Group II developed potassium deficiency with alkalosis and Group III developed potassium deficiency without alkalosis. Histologic changes in renal tubular cells were demonstrated in both groups.

Concentration tests were made at 3 and 11 days. A comparable defect in concentrating ability was demonstrated in both experimental groups at 3 days, and a progression of this defect was observed at 11 days.

Dilution studies were made at 10 days, and no defect was observed.

Similar studies were carried out in animals that had received the electrolyte-deficient diet for 100 days. A considerable defect in concentrating ability and a measurable defect in diluting ability were demonstrated. Upon restoring the deficient electrolyte to the diets, the diluting defect was corrected in two days. There was some improvement in the concentrating defect in three days but evidence of its continued presence persisted for two weeks after the animals had received "repair solution."

It is concluded that potassium deficiency and not alkalosis is critical in the development of the concentrating defect. The dissociation of the diluting defect from the concentrating defect suggests that these processes occur separately. If a correlation exists between the locus of the histologic changes in the tubules and the concentrating defect described, one might then infer that dilution occurs at a separate locus.

Congenital Pernicious Anemia. JOSEPH A. LITTLE,* THOMAS D. STEVENSON,* and LESLIE W. LANGLEY,* Louisville. (Introduced by William A. Brodsky)

Pernicious anemia is rare in infancy and childhood. Of the previously reported cases, the majority have been diagnosed on clinical grounds alone. However, the unequivocal diagnosis of pernicious anemia depends upon demonstration of the absence of the intrinsic factor from the gastric secretions.

We have studied a 6-year-old Negro male with a chronic recurrent macrocytic anemia. Vitamin B_{12} deficiency was demonstrated by microbiological assay. The absence of the intrinsic factor was proven by the uptake test of Schilling, utilizing radioactive Co^{60} labelled vitamin B_{12}. The presence of normal gastric acidity and pepsin was established. The patient's gastric juice when fed to an adult patient with known pernicious anemia failed to induce absorption of radioactive vitamin B_{12}. There was no evidence of neurological abnormalities.

Macrocytic anemia occurred after the first year of life in all cases in children with proved pernicious anemia. We have data that demonstrate the normal placental transfer of vitamin B_{12}. Therefore, vitamin B_{12} deficiency is manifested only after exhaustion of the normal body stores. In children we assume that this specific and selective defect in the gastric secretion must be congenital in origin.

Also, it is interesting to speculate on the effect of this vitamin deficiency on growth and development.

Our patient is of small stature despite a history of "normal" diet and a physically "normal" family. In each instance when vitamin B_{12} was given parenterally, a large weight gain ensued. There is no indication of any mental retardation.

The implications of these findings will be discussed.

Stable Iodine Poverty in Hypothyroidism with and Without Goiter and in Colloid Goiter: New Method of Analysis. Wm. A. Reilly, H. L. Helwig,* and K. G. Scott,* with the Technical Assistance of James N. Castle and Charles Louie, California.

The question of iodine poverty in hypothyroidism and colloid goiter was investigated by a new method for analyzing stable iodine (I^{127}).

Stable urinary iodine (I^{127}) was concentrated by passage through a AgCl column; the I in the AgI was liberated as iodate by Br_2 water; this was converted into I_2 and quantitated spectrophotometrically. This method proved to be rapid and reliable. From the urinary I^{131}/I^{127} ratio, estimations were made of I^{127} level of plasma, thyroid uptake and extrathyroidal pool.

Results—Mean 6° Figures—21 Children

	Plasma γ/L at 6°	Thyroid Uptake γ/kG. for 6°	Extra-thyroidal pool γ/kg. 6°	Urine Excretion 6°	γ 24°
Euthyroid 7	4.04 Norm.	1.13 Norm.	4.04 Norm.	20.7 Norm.	69.9 Norm.
Hypothyroid Athy. or Acq. 5	Decr.	Decr.	Decr.	Decr.	Decr.
Goitrous 5 (11 Det'ns.)	Decr.	Incr.	Decr.	Decr.	Norm.
Colloid Goiter 4	Decr.	Decr.	Decr.	? Norm.	Decr.

These results showed that in classical hypothyroidism and colloid goiter I^{127} pool, plasma level, and thyroid uptake were lower than normal. In goitrous hypothyroidism the results were the same except that thyroid uptake was greatly increased. In the euthyroid state comparisons with adults (*39*) showed that children had lower plasma levels but an increased pool and thyroid uptake. Discussion of iodine supply in the body and thyroid function.

Summary.—A short reliable method is presented for measuring urinary stable iodine. In hypothyroidism and colloid goiter this has shown iodine poverty in plasma, thyroid uptake and extra-thyroidal pool. Goitrous hypothyroids, while iodine poor, showed the expected increased thyroid uptake of I^{127}.

Partial Characterization of C_{21} Steroids in the Urines of Children with Adrenogenital Syndrome. Hortense M. Gandy,* Rochester. (Introduced by Gilbert Forbes)

This study was undertaken in order to more closely define the defect in C_{21} synthesis in patients with the adrenogenital syndrome. The urinary excretion pattern of C_{21} steroids was studied quantitatively before and during the administration of adrenocorticotropin and cortisone. The method of determination of this excretion pattern consisted of (a) glucuronidase hydrolysis followed by ether extraction, (b) determination of total alpha ketols of the neutral extracts with blue tetrazolium and (c) separation of the individual alpha ketolic steroids by paper chromatography (as described by Burton et al). The urinary metabolites were further characterized on paper for (a) ultraviolet absorption, (b) the presence of alpha ketols, (c) alpha and beta saturation, (d) the presence of ketones and (e) hydroxylation. Absorption maxima in methanol and sulfuric acid chromogen spectra were also studied.

Urinary metabolites tentatively identified are tetrahydrohydrocortisone, hydrocortisone and tetrahydro S; other alpha ketol metabolites have been isolated but specific identity is incomplete. Jailer et al and Bayliss et al have reported that there is no appreciable rise in urinary corticoids following adrenocorticotropin. We have noted that total urinary corticoids and their C_{21} steroid fractions are increased following the administration of adrenocorticotropin.

We have thus concluded that if there is a block in the formation of hydrocortisone by the adrenals of these patients, the block cannot be complete. While such an incomplete block may be responsible for increased adrenocorticotropin secretion by the pituitary, this does not cause maximal adrenal stimulation. These findings are also compatible with the theory of the existence of several types of adrenocorticotropin.

Sensitivity to Posture in Cyanotic Congenital Heart Disease as Studied by Instantaneous Respiratory Gas Measurements. PAUL R. LURIE, Indiana.

The abrupt responses of patients with tetralogy of Fallot to favorable and unfavorable postures have long been recognized. Our earlier work has suggested that this posture-sensitivity depends upon a constellation of physiological characteristics peculiar to tetralogy which leads to exaggeration of the usual effect of gravity upon venous return to the heart. These essential factors for posture-sensitivity are right to left shunt, reduced pulmonary blood flow, increased systemic flow at horizontal rest, and absence of tendency to congestive heart failure.

Cyanotic congenital malformations of the heart which fail to meet these requirements are not posture-sensitive. This distinction is of practical importance, since absence of posture-sensitivity indicates a tendency to congestive failure or an abundant pulmonary blood flow, either of which would decrease the likelihood of success of a systemic-pulmonary arterial shunt operation.

In the past, clinical observations of cyanotic patients have been made during rest and exercise, and during recovery in favorable postures such as squatting and in unfavorable postures such as quiet standing. These reactions have also been observed with the ear oximeter. The present work brings to bear upon this problem the further observation permitted by the instantaneous CO_2 analyzer and the pneumotachygraph.

Fifteen patients with cyanotic congenital heart disease were studied by ear oximetry and continuous measurement of volume and CO_2 content of respired air. These measurements were made during exercise on a treadmill and during recovery in the standing position. After a rest, the measurements were repeated during an identical exercise and during recovery in the squatting position. Similar studies were made of a group of normals.

In normals the increased CO_2 production during exercise resulted in increased ventilatory volume and a small rise in alveolar CO_2 tension. Arterial O_2 saturation was increased slightly by hyperventilation. Similar courses of recovery were observed in the standing and squatting postures.

In all the cyanotic patients too, ventilation increased during exercise. The alveolar pCO_2 fell and arterial O_2 saturation fell. Since the arterial hypoxemia was by definition in these cases due to shunt of systemic venous blood into the systemic arterial bed, it followed that such a fall in oxygen saturation was accompanied by a relative increase in arterial pCO_2. The lowering alveolar pCO_2 was the result of complementary factors: (1) hyperventilation due to the elevated arterial pCO_2 brought in a greater volume of air to dilute the CO_2 in the alveoli; (2) to the extent that CO_2 bypassed the lungs, the available CO_2 flowing into the lungs for equilibration with alveolar air failed to increase in direct proportion to the increase in CO_2 production.

The course of recovery in non-posture-sensitive patients was similar in both the standing and squatting positions. This consisted of a gradual return toward normal of the arterial O_2 saturation, alveolar pCO_2, and ventilatory volume.

In contrast to this, the course of recovery of the posture-sensitive patients was influenced by posture in the following ways: On standing, they showed a prolonged low alveolar pCO_2, a prolonged gradual increase in arterial O_2 saturation, and a slow decrease in ventilatory volume. On squatting, there was an abrupt and sustained rise in alveolar pCO_2 and an increase of arterial O_2 saturation which followed rapidly and reached a higher plateau than was reached when standing. Ventilatory volume decreased rapidly, following a course inverse to that of arterial O_2 saturation. The sudden rise of alveolar pCO_2 was explained as the result of increased venous return immediately increasing the volume of flow of CO_2-laden blood into the lungs; it was not primarily the result of decreased ventilation as it clearly preceded this.

These new observations fit with and corroborate our earlier theory of the mechanism of postural effects. The method used determines posture-sensitivity in a more objective way than heretofore possible, thus offering an improved means of selection of candidates for systemic-pulmonary shunt surgery in cyanotic congenital heart disease.

Diagnostic Significance of Bronchial Flora of Patients with Fibrocystic Disease of the Pancreas. NANCY NAN HUANG,* Temple. (Introduced by Robert H. High)

The results of cultures of the nasopharyngeal and bronchial secretions from 29 patients with fibrocystic disease of the pancreas have been compared with those obtained from 22 patients with chronic bronchopulmonary disease of various causes other than fibrocystic disease.

In order to avoid undue emphasis on the frequency of the bacteria repeatedly cultured from a few patients, in whom as many as 25 cultures might be obtained, the results have been analyzed by the following method. Any culture which contained a given organism, either singly or in combination with others, is designated as comprising a single bacterial pattern. For example, if Pseudomonas aeruginosa were to be isolated in pure culture on one occasion, and later in combination with hemolytic Staphylococcus aureus, from the same patient, the Pseudomonas would be considered as having occurred in two bacterial patterns. On the contrary, if Pseudomonas aeruginosa were to be isolated in pure culture from a single patient on

20 occasions, it would be considered as having occurred in only one bacterial pattern.

There is a striking difference in the distribution of the bacterial flora from patients with fibrocystic disease of the pancreas when compared with that from patients with other types of chronic bronchopulmonary disease. This difference is apparent regardless of the method of analysis, i. e., on the basis of bacterial patterns, initial cultures alone or inclusion of all organisms obtained in all cultures.

The prevalence of intestinal types of Gram-negative bacilli (Pseudomonas aeruginosa, coliform and B. proteus) in bronchial secretions of patients with fibrocystic disease of the pancreas is in contrast to the infrequent occurrence of these organisms in patients without fibrocystic disease. Thus 60% of the bacterial patterns in bronchial secretions from patients with fibrocystic disease of the pancreas contained such bacilli, whereas only 10% of those from patients with other types of chronic bronchopulmonary disease contained these organisms. Hemolytic Staphylococcus aureus also occurred more frequently in cultures from the nasopharynx and bronchi of patients with fibrocystic disease than in the other patients, but this difference is not statistically significant.

Cultures from the bronchial secretions of patients with fibrocystic disease of the pancreas yielded no pathogens in only two cases, whereas negative nasopharyngeal cultures were obtained from 10 such patients. In infants and children without fibrocystic disease, however, this discrepancy between the results of nasopharyngeal and bronchial cultures was not apparent. Bronchial cultures would appear therefore to be more reliable than nasopharyngeal ones in patients with fibrocystic disease of the pancreas.

The antibiotic sensitivity of the pathogens isolated from the patients with fibrocystic disease of the pancreas and the effect of antibiotic therapy on the bacteriologic findings will be discussed.

Serum samples have been obtained from a few patients with fibrocystic disease of the pancreas. These are being tested for their antibody titer against Pseudomonas aeruginosa.

Tissue Electrolyte Composition in Experimental Nephrosis of Rats and After DCA Administration. DONALD GRIBETZ, MARVIN F. LEAVITT,* and DEMITRA PANDIRI,* Mt. Sinai Hospital.

Electrolyte and water analyses of muscle, skin, cortical marrow-free bone, tendon, and plasma were performed on three groups of rats: (1) animals rendered "nephrotic" by rabbit anti-rat kidney serum technique; (2) animals treated with DCA (3 mg. daily for 6 days); (3) normal animals used as controls.

Compared with the normal rats, the "nephrotic" animals showed a mean 50% increase in sodium and chloride content of muscle with slight diminution in potassium content. The water content coincidentally increased from 77.6% of total weight in the normals to 79.1% in the "nephrotics," an increase which corresponds exactly to a 50% gain in extracellular volume. Changes in skin were very similar with comparable increases in salt and water, whereas bone and tendon showed no detectable changes in electrolyte and water content. The plasma of the "nephrotic" animals showed typical cholesterol and protein changes of nephrosis, but no changes in electrolyte composition were detected.

The DCA treated animals exhibited an increase of 15% in sodium and chloride content of muscle when compared to their normals and a marked diminution of potassium content approximating 15%. Water content rose from 75.6% to 76.3% of wet tissue weight. In this group, in contrast to the "nephrotics," no detectable changes were present in skin. Bone and tendon analyses, as in the "nephrotics," showed no change from the normal. Plasma reflected the characteristic hypochloremic, hypokalemi: alkaloses.

These data indicate that experimental nephrosis is characterized by simple retention of Na, Cl, and water in isoosmotic proportions and that this fluid accumulates in those tissues which offer the least resistance to expansion of the extracellular fluid, tissues such as muscle and skin. The fall in cellular potassium is very small and there is no other evidence of primary alterations in cellular electrolyte or water content. The excess stores of salt in bone and tendon, which are mobile after such stimuli as acute acidosis, do not move into the extracellular fluid in "nephrotic" or DCA-induced edema.

The greater potassium depletion and lesser salt retention induced by DCA administration as compared with that noted in the "nephrotic" animals suggests that "DCA-like" salt retaining hormones of the adrenal gland, per se, do not produce the tissue changes of experimental "nephrosis."

Studies of Blood Protoporphyrin and Iron in Lead Poisoning. R. JANET WATSON,* HERBERT C. LICHTMAN,* ELISABETH DECKER,* and FELIX FELDMAN,* State Univ. of N. Y., New York. (Introduced by Richard Day)

Hematologic studies and determinations of free erythrocyte protoporphyrin (FEP), and plasma iron and copper were done in 11 children, aged 1½ to 3 years with acute lead poisoning. All patients had a microcytic hypochromic type of anemia, with hemoglobin values ranging from 6.0 to 10.0 gm. %. In 7 of the 11 there was a reticulocytosis of 2.7 to 10.8%. Stippling of the red cells was seen in eight of the cases. The FEP was markedly elevated in all, with values ranging from 1191 to 4320γ % (normal 22 to 175γ %). The plasma copper was normal or increased, with

values of 81 to 304γ %. The plasma iron was low (16.6 to 46.6γ %), the per cent saturation was decreased (5.9 to 20.2), and the total iron binding capacity (TIBC) was normal or decreased (190 to 425γ %).

The anemia was morphologically characteristic of a nutritional iron deficiency anemia which is common in the age group of the patients in this series. The presence of iron deficiency may have been a predisposing factor in the development of pica and the ingestion of the lead. The normal TIBC and the elevated reticulocyte counts may be attributed to the lead poisoning, since elevated TIBC and normal reticulocytes are seen in iron deficiency. The anemia responded very satisfactorily to the administration of oral iron coincident with treatment of the lead poisoning with intravenous calcium versenate.

Since FEP values do not usually exceed 600γ % in iron deficiency, the very high values seen in these patients are presumed to be the result of lead poisoning. Indeed, no other condition is known to raise these values to such high levels. The increased urinary excretion of coproporphyrin III in lead poisoning in humans is well known, but the exact tissue source has not been definitely ascertained. The high FEP in these patients indicates that one of the tissue sources may be the erythrocyte, the FEP being presumably manufactured along with coproporphyrin III as a by-product in normal heme synthesis. This is further evidence of abnormal porphyrin metabolism in lead poisoning.

Some Relations of Tissue Proteins to Serum Globulins. S. D. Yeh,* W. F. Seip,* and F. W. Barnes Jr., with the aid of T. Prezios and R. Rutherford, Johns Hopkins.

Studies elsewhere and in this laboratory of the effects on tissue of damaging agents permitted the announcement of a simple axiomatic principle of restorative response, namely, that if a cell is partially depleted of essential constituents that cell or others will attempt to restore the depleted substances as quickly as possible. Experimental ramifications of this led to the prediction that most of the tissues of man and many animals continually yield part of their normal protein constituents to the intercellular fluids and to the blood as globulins. This implied that these globulins are involved in a continual cycle of recirculation between the blood and the cells of the tissue of origin. It was further suggested that the concentration of each tissue component in serum is capable of wide and largely independent variation in disease states.

In recent years some curious facts, explainable by the above prediction, have been found about the behavior of serum proteins. Serum proteins are involved in a rapid dynamic equilibrium with certain cells or tissues of the body which must be revisited continuously by the serum proteins. Globulins of the blood have been found to fluctuate widely in disease and certain components of globulins have been found to vary independently in many diseases. Serum globulins and albumin pass into an extravascular compartment at least equal to that of the blood. Serum fractions have been found widespread in nuclei and cytoplasm of many tissues. Considerable evidence exists for a continual circulation of serum proteins from vascular compartments through intercellular spaces into cells and back to the blood.

Partial confirmation of the above predictions made in this laboratory is here reported by demonstration of varying concentrations of protein components of the tissues in human serum through use of rabbit antisera giving specific precipitins with extracts of individual human organs. Previous work by a number of workers has shown that organ and tissue specificity does exist and specific antisera have been made. Specific antisera have been made even to myosin of skeletal and cardiac muscle separately.

Confirmatory evidence from several kinds of sources will be reported, and the significance of these findings in terms of tissue response under various stresses, of a possible role of circulating globulins in specific protection against agents capable of attacking cell targets, and of implications in the field of tissue interaction through circulating representatives of each tissue under varying conditions will be mentioned.

Increased Tissue Histamine in Urticaria Pigmentosa: Preliminary Observations on the Site of the Biochemical Error. Lytt I. Gardner and Artelissa A. Tice,* State University of New York, Syracuse.

It has been found in several laboratories that mast cells contain very large concentrations both of histamine and of heparin. It is now believed that the organic acid heparin is the basophilic material of mast cell granules, and that histamine is the organic base with which the heparin is associated intracellularly. The syndrome of urticaria pigmentosa is characterized by localized or generalized hyperplasia of mast cells. We have had the opportunity to study tissue from a boy with urticaria pigmentosa who developed an urticarial rash at age 2 months and who finally died with intraperitoneal hemorrhage at age 5 years.

Trichloracetic acid extracts of liver and spleen were subjected to ascending chromatography on paper, using the N-butanol:acetic acid:water system of Slotta. Histamine was determined by the diazo reagent of Rosenthal and Tabor. Estimation of histamine concentration in terms of histamine base revealed approximately 1250 μg/gm. wet liver, and slightly less in the spleen. Analysis of normal liver tissue revealed only 10 to 12μg/gm. wet liver. The

chromatographic pattern of the urticaria pigmentosa liver was virtually identical to that obtained by West and Riley in their studies of dog mastocytoma tissue. Even higher values for histamine were obtained independently on the urticaria pigmentosa liver and spleen tissue by Dr. Helen Tredway Graham of Washington University using the method of Lowry and others. Drs. William J. Waters and Perpetua Lacson have measured the concentration of heparin-like material in the liver of this case and have found it also to be very greatly increased.

It seems most likely that the metabolic error in urticaria pigmentosa is congenital absence or inadequacy of an enzyme involved in the degradation of histamine or of heparin. There are at present no data to indicate whether the enzymatic defect is primary to the intermediary catabolic sequence of histamine or of heparin. The proliferation of mast cells may be a homeostatic reaction to provide an intracellular "storage" place for these compounds, which are so potent when free in plasma.

Studies on Familial Nephrosis: Evidence for a Unitarian Concept. ROBERT L. VERNIER,* MARILYN G. FARQUHAR,* JOEL G. BRUNSON,* and ROBERT A. GOOD, Minnesota.

The etiology, pathogenesis, and natural history of lipoid nephrosis are enigmatic. Much dispute concerning the relationship between nephrosis, chronic nephritis and other forms of chronic renal disease in childhood still exists. In an effort to gain insight into the basic disease mechanisms and inter-relationships between nephrosis and other forms of renal disease in children, an extensive comparative study employing clinical observation, discrete renal function tests, and renal biopsy has been undertaken. The biopsies, obtained by both needle and open techniques, have been subjected to pathologic study using both light microscopy and electron microscopy. Thus far biopsy material has been obtained and studied from 30 children with various renal diseases including lipoid nephrosis, chronic glomerulonephritis, chronic nephritis with nephrotic manifestations, Henoch, Schoenlein's disease and lupus erythematosus, Particularly contributory have been the studies carried out in patients with "familial nephrosis." Lipoid nephrosis occasionally occurs as a familial disease (Fanconi). During the past year we have observed multiple cases of nephrosis within each of four families. Individually cases of "familial nephrosis" cannot be distinguished from the sporadic disease. However, a varied spectrum of the nephrotic syndrome occurred among the four children in one family. Intensive study of this family was undertaken in an effort to gain insight into the pathological spectrum and the natural history of nephrosis in man.

Clinical case material included the following: Case I, male, age 6 years, onset at 4 months, death at age 7, renal insufficiency. Case II, male, age 5, transient "pure" nephrosis. Case III, female, age 3, onset 4 months, typical chronic nephrotic syndrome. Case IV, female, age 3 months, onset at birth, typical "pure" nephrosis. Father, mother, and half-brother are normal. The mother had "nephritis" in her youth and has "pre-eclampsia" with each pregnancy.

The following studies were performed: routine clinical and laboratory study, serial electrophoretic patterns, serial bone marrow biopsies, discrete renal function studies, adrenal response tests, and renal biopsies. Renal biopsies were studied with hematoxylin-eosin, azocarmine, and periodic acid (Schiff) stains. The findings were severe chronic glomerulonephritis in Case I, subacute glomerulonephritis in Case III, and normal architecture in Case IV. Assuming a single etiologic basis for these cases we must conclude that familial nephrosis may be chronic, progressive, and reflected clinically and pathologically in a variety of patterns.

Using electron microscopy a striking lesion of the epithelial layer of the glomerular tuft is present in all the children regardless of the clinical phase of the disease or state of the pathologic process as observed by light microscopy. The lesion consists of apparent distortion and obliteration of the epithelial podocytes resulting in smudging of the epithelial cytoplasm along the basement membrane.

We interpret this observation together with the finding of multiple pathological and clinical phases of nephrosis within a single family as evidence that nephrotic syndrome with single etiologic basis may have a multiplicity of clinical and pathological expressions. These may be unified by a pathological process recognizable at the submicroscopic level with the electron microscope.

The Endocrine Regulation of Fat Mobilization and Utilization: I. The Effect of Hypophysectomy. LEROY W. MATTHEWS,* SAMUEL SPECTOR, and JOY LEMM,* Western Reserve.

Specific effects of hormones and of hormone deficiencies on fat metabolism in vivo are for the most part unknown. Most of the work done in the past has been based on the effects of hormones or hormone deficiencies on blood lipid levels, liver fat content, and ketogenesis. Decreased fat content of the blood and liver, increased depot fat, and resistance to ketosis are characteristic of the hypophysectomized rat. From these findings in the past, it has been concluded that deficiency of the pituitary hormones results in a depression of fat mobilization and utilization.

The utilization of C^{14} labeled trilaurin and tripalmitin administered by both oral and intravenous routes and the turnover rate of total body fat has been studied in normal and hypophysectomized rats. In spite of a 35% reduction in the metabolic rate of the hypophysectomized rats, they

were found to utilize significantly more fat per mM of CO_2 expired than normal rats. This increased utilization of exogenous fat varied from 14% to 97% for the various fats and routes of administration and was found in both fasting and fed rats.

The turnover rate of endogenous total body fat was found to be almost twice as rapid in the hypophysectomized rats and the half-life of total body fat 9.0±1.33 days as compared with 14.9± 0.15 days in the normal rats. The fat content of the hypophysectomized rats averaged 11.12 gm./ 100 gm. body weight compared with 8.29 gm/100 gm. body weight in the control rats. When both of these factors are taken into consideration, the hypophysectomized rats are found to utilize 0.86± 0.13 gm. of endogenous fat per 100 gm. body weight per day and the normal rats only 0.38± 0.04 gm. of endogenous fat per 100 gm. body weight per day.

Our findings raise considerable doubt as to the value of hyperlipemia, fatty liver or ketosis as an index of total fat utilization. This will be more fully discussed.

Autotransfusion of Newborns. THOMAS A. PRIER* and MARION W. HOOD,* Tulane. (Introduced by R. V. Platou)

For a variety of reasons, many neonates evidence need for early transfusion of whole blood. No better-matched blood is available than the infant's own, a supply of which is ordinarily left behind in the placenta.

A simple and safe technique for aseptic collection of this blood (at the time of delivery) will be described. Using equipment readily available in most hospitals, from 50 to 200 cc. of placental blood can easily be collected aseptically, even with "contaminated" deliveries. Appropriate culture checks to assure sterility will also be described. This study incidentally casts some doubt on certain widely-held views relative to causes and incidence of bacteremia in newborn infants.

Total Body Electrolyte, Intracellular Concentration and Extracellular Volume in the Rat. DONALD B. CHEEK and CLARK D. WEST, Cincinnati.

Total body electrolyte, nitrogen, and water are related to lean body weight or fat free dry solid of the rat over a wide weight range (rats of 70 to 410 gm.). The regression equations so derived demonstrate a small standard error of the estimate and are of use in the investigation of abnormalities in electrolyte metabolism. An effort has been made to correctly define intra- and extracellular volume in the whole body of the rat. From available data correction of the chloride space has been made for intracellular erythrocyte chloride. The determination of total body collagen, collagen chloride, and water have allowed an estimate of the correction factor for connective tissue chloride which is at a higher concentration than a serum ultrafiltrate. The reliability of the corrected Cl space as an accurate index of extracellular volume has been assessed by calculating the amount of sodium in the extracellular fluid. The bone and cell sodium of the rat have been determined and subtracted from the total body sodium to give the extracellular sodium. From available data using the constant and prolonged infusion of inulin, the correct amount of intracellular sodium of muscle can be calculated and data exist with respect to red cell sodium content. The area in doubt is the visceral organs and here the constant infusion of inulin into rats and the comparison of the sodium and inulin space have allowed the determination of sodium in visceral cells. From the Na/Ca ratio in bone and total body calcium the amount of sodium in bone may be calculated. With the assessment of extra- and intracellular volumes in the rat the concentration of intracellular electrolyte can be calculated from the total body content.

Methodologic Observations Pertaining to the Diagnosis of Progressive Loss of Pancreatic Function. ROBERT G. FRAZIER,* Iowa. (Introduced by Charles May)

That progressive loss of pancreatic function may occur in patients with cystic fibrosis of the pancreas can readily be assumed. It is important to establish the frequency with which this occurs. Progressive loss of pancreatic function has been substantiated largely on the basis of the gelatin viscosity method. This method uses the Ostwald viscosimeter to measure the change in viscosity of a gelatin substrate and is described as being more simple and precise than the traditional Andersen-Early method. This paper emphasizes the need for sound methodology by evaluating the accuracy of the gelatin viscosity test and comparing data obtained by the two methods.

Solutions of proteolytic enzymes in various concentrations were used to digest gelatin substrates so that viscosity times ranged from 40 to 80 seconds after one hour of incubation using the standard conditions described for this test. Solutions with a final viscosity time of less than 70 seconds would no longer gel when refrigerated as done in the Andersen-Early method. This approximates the figure of 80 seconds which is the desired endpoint of the gelatin viscosity test. Because of the similarity in substrates and test conditions in these two methods it was expected that the calculated data would also be similar. The nature of this correspondence and the range of precision obtained by published data and data from our laboratory will be illustrated.

Calculation of the enzyme activity by the standard equation for a first order reaction is based on

two assumptions which are not fulfilled by the conditions of the gelatin viscosity test. The calculation should be corrected for the viscosity of water in the gelatin solution and should be based on a period of time when the digestion products are proportional to the enzyme concentration. After one hour of incubation the digestion products are no longer proportional to the concentration of enzyme. The magnitude of the errors so introduced and the degree to which they can be minimized will be shown.

The published data purporting to show progressive loss of pancreatic function have relied in many cases on the gelatin viscosity test and ignored results of the Andersen-Early method. Data presented here show that the potential error of the gelatin viscosity method is as great as that in the Andersen-Early method. For use as a diagnostic test the Andersen-Early test is much simpler than the gelatin viscosity test as it has been described. Greater accuracy can be obtained by the gelatin viscosity method if performed as originally described by Northrop and Hussey but at greater pains.

Biochemical Lesions Observed in Experimentally Induced Renal Tubular Disease in Rats. RUTH T. GROSS,* CAROLYN F. PIEL, and HAROLD HARPER,* Stanford and California.

The identification of renal tubular diseases in man has been aided by the application of recent biochemical techniques and increased knowledge of renal physiology. Not only have specific clinical syndromes been described, but in recent years similar derangements have been produced in animals by the use of drugs which act as enzymatic blocking agents. Berliner in 1950 demonstrated that maleic acid administered to acidotic dogs abolished their capacity to excrete an acid urine and led to increased excretion of endogenous phosphate. Harrison in 1954 used this drug in rats to produce renal glycosuria, phosphaturia, and aminoaciduria, a symptom triad which is found also in a congenital metabolic defect in man known as the de Toni-Fanconi syndrome. The purpose of this study is to present detailed biochemical observations on rats poisoned with maleic acid in an attempt to clarify the action of this drug.

Rats have been poisoned with varying doses of maleic acid in order to confirm Harrison's findings of phosphaturia, glycosuria, aminoaciduria, and decreased excretion of citric acid. Observations have also been made on the blood levels of glucose, citric acid, and lactic acid and on the levels of citric acid and lactic acid in the tissues. These findings have been compared with similar observations on rats poisoned with sodium fluoroacetate, a substance known to block the Krebs cycle just beyond citric acid by the competitive inhibition of aconitase. Maleic acid, like sodium fluoracetate, led to accumulation of both citric acid and lactic acid in the blood.

The above findings will be presented and the implications regarding the site of action of maleic acid and its role in experimental production of renal tubular disease will be discussed.

The Biphasic Effect of Cortisone on RNA Metabolism. CHARLES U. LOWE and ROYDEN RAND,* Buffalo.

Histological data and in vitro experiments indicate that administration of cortisone to rats for 5 days results in an apparent alteration in structure of a portion of the hepatic ribonucleic acid (RNA) of liver. This effect is believed to be due to the presence of an RNA depolymerase in the livers of cortisone-treated animals.

The present experiments were undertaken to examine the mechanisms whereby cortisone affects RNA metabolism. Structural change in RNA was indicated by decreased yield of polymerized RNA and increased acid solubility of RNA when chemical isolation was conducted at 20 C. Alteration in technique to the extent of performing isolation at 0 C permitted isolation of normal amounts of polymerized RNA from mitochondria and microsomes of cortisone rat livers. However, in cortisone liver, incorporation of P^{32} on Day 5 by the Mit-RNA prepared by the cold technique was decreased by 50% in comparison with the normal. These results suggest that although RNA synthesis in mitochondria was decreased at five days, there must have been a period prior to this time when RNA was increased in amount. In fact, it was observed that after two days of cortisone administration the RNA/hepatocyte was increased by 30%. On subsequent days there was a precipitous fall until on the 5th day the values were similar to those observed in the normal.

These results indicate that the effect of cortisone on RNA content of liver has two phases. The first phase includes a period of marked RNA accumulation; this is followed by a rapid disappearance of RNA during which the action of a depolymerase is the predominant biochemical phenomenon. Since protein synthesis is thought to be related to RNA synthesis it is possible that events during the first phase are related to protein anabolism and those in the second phase to protein catabolism.

Relationship Between Hematocrit and Intraventricular Hemorrhage in Premature Infants. WILLIAM A. BLANC,* ROY BROWN,* and WILLIAM A. SILVERMAN, Columbia.

The present report was prompted by the study of serial hematocrit determinations on 60 premature infants. Before the present study began, 10 infants who had not been subjected to surgical procedures or had not shown any evidence of ex-

ternal blood loss died and had postmortem examination of the brain performed. A significant drop in hematocrit ratio occurred in 4 of these 10 babies, and intraventricular hemorrhage was subsequently demonstrated at autopsy in these 4 infants. The variation of the hematocrit in the babies without brain hemorrhage remained in the range observed among the survivors.

A drop was observed after the third day in these four patients, thus suggesting the postnatal occurrence of intraventricular hemorrhage. This was in agreement with the clinical impressions. The pathological data, such as the finding of fresh blood, absence of hemosiderin or hematoidin and inflammatory reaction, also supported the view that the hemorrhages were fresh.

When the amount of intracranial blood loss is evaluated at postmortem and compared with the estimated blood volume, it can be shown that the estimated volume of blood loss is sufficient to explain the hematocrit drop.

These preliminary results were based on macrohematocrit determinations on venous blood. A systematic study consisting of serial hematocrit determination on capillary blood with a micro method was started. A comparison between macro and micro hematocrit, the mean hematocrit values, and mean variation will be reported.

It is felt that within the error of the method the capillary hematocrit may be of value in determining the antemortem clinical diagnosis of intraventricular hemorrhage in premature infants. The definite proof of a free interval between birth and occurrence of intraventricular hemorrhage may encourage further studies and admit the possibility of therapy.

The Cells Seen in the Pharyngeal Smears from Three-Day-Old Infants. ALFRED L. FLORMAN, CHRISTINE I. PEGG,* and ALEXANDER S. ROSEN,* North Shore Hospital, Manhasset, N. Y.

The usefulness of the pharyngeal smear in differentiating between the follicles of benign pharyngeal erythema in the newborn and more serious throat lesions which they may mimic was demonstrated in a report read by title to this Society last year. The present study was undertaken in order to learn what cells might be expected to be found normally in pharyngeal smears in the neonatal period of life.

The throats of 200 infants were examined on the third day of life and smears made from the pharynx with cotton swabs. These swabs were immediately immersed in Papanicolaou's fixative and stained with his technique. The epithelial cells seen were classified as superficial or cornified, parabasal or basal. Smears from individual infants almost always showed some cells of each variety, although usually parabasal cells either alone or combined with one of the other types predominated. Photomicrographs will be shown to illustrate this basic pattern, and to compare with smears made from older infants. There were 42 newborns in this group of 200, who had benign pharyngeal erythema and follicle formation, and 18 who had gynocomastia. The distribution of cell types seen in the pharyngeal smears from each of these two groups will be compared with that in the other newborns. Bacteria were almost always found in smears from 3-day-old infants, but inflammatory cells were rarely seen in significant numbers. Cytoplasmic inclusion bodies were present in some of the superficial epithelial cells and the female sex chromatin as described by Moore and Barr could be found in epithelial cell nuclei of female infants.

Streptococcus Carrier Studies in Children. HARRIS D. RILEY JR.,* ROBERT W. QUINN,* and FLOYD W. DENNY JR., Vanderbilt.

Since the epidemiology of streptococcal infections in civilian population is poorly understood, a study was designed to investigate in children carriers of β-hemolytic streptococci. Findings for the first two years of this study will be reported.

Approximately 175 third and fourth grade students from three city schools for white children in Nashville, Tenn., were studied during each of the academic years, 1953-54 and 1954-55. The three schools were located in widely separated areas of the city which varied markedly in socioeconomic levels. Throat cultures were obtained weekly during the first year and biweekly during the second year of the study. Strains of β-hemolytic streptococci isolated were classified by standard methods.

Carrier rates were strikingly high and different for each school throughout the study. Rates during 1953-54 were significantly higher than those during 1954-55. In 1953-54 the maximal rates were between 41% and 60% and in 1954-55 between 26% and 42%. The cumulative percentages of children carrying β-hemolytic streptococci ranged from 75% to 88% in the first study-year, and from 57% to 60% during the second study-year.

Eighty-four per cent of the streptococci isolated were group A, and, of these, 48% could be classified by serological type. The principal types isolated were types 1, 3, 4, 5, 6, and 12. The distribution of types were different in each of the three schools during each of the study-years.

Efforts were made to correlate these results with the environmental conditions in the schools and homes of the students, with weather conditions, and with the presence or absence of tonsils. During each of the study-years the highest carrier rates occurred in the school with the highest socioeconomic standards. Weather differences did not explain the variation in carrier rates for the two

years. In the first year of this investigation there was no difference in the carrier rates for children with and without tonsils, but in the second year the rates were lower in the tonsillectomized children. The significance and implications of these extremely high and variable Streptococcus carrier rates in a southern city will be discussed.

The Cardiostatic Effect of Certain Ions and Compounds on the Isolated Perfused Cat Heart. DORIS H. MERRITT,* WILL C. SEALY,* and JEROME S. HARRIS, Duke.

Certain ions have long been known to have cardiostatic properties. That an excess of potassium is capable of stopping the heart in diastole and that an excess of calcium can do the same in systole was first described by Ringer in 1883. Because of the obvious surgical advantages to be gained from having a solution available which can induce immediate cardiac arrest when injected directly into the coronary circulation and can be washed out rapidly leaving the beat unchanged, the effect of these and other ions and compounds (certain of which have been reported to have antifibrillatory properties) were studied on the isolated cat heart in a Langendorff-type perfusion apparatus. The optimal solution proved to be a mixture of magnesium sulfate and potassium citrate with a small amount of an antifibrillatory drug such as Pyribenzamine, Benadryl, Doryl, or Prostigmin. This mixture caused a prompt cessation of the cardiac beat and of electrocardiographic activity. It could be readily perfused out to allow an equally prompt return to a normal rate and rhythm without signs of anoxic injury. When a fibrillating heart was arrested by this method, a normal beat returned as the solution was perfused out. The method has also been applied successfully in producing temporary cardiac arrest in the intact dog, with survival of the animal after 14 minutes of cardiac arrest.

Neomycin Aerosol in the Pulmonary Component of Cystic Fibrosis of the Pancreas. G. E. GIBBS, Nebraska.

Parenteral use of neomycin presents serious hazards of nephrotoxicity and ototoxicity. Topical and oral use of this drug, however, has become common. In the present study, neomycin aerosol has been tried as a possible topical treatment of the bronchitis in cystic fibrosis of the pancreas.

Neomycin sulfate was nebulized in a dosage of 55 to 80 mg/kg/day, divided into four to six treatments per day. Seven trials were made, involving four patients. In each case the apparently significant organism was Staphylococcus showing some in-vitro sensitivity to neomycin. Definitely favorable results were obtained in five of the seven trials. No definite evidence of toxic effect of the drug was obtained in any case.

Paroxysmal Supraventricular Tachycardia with Special Reference to Treatment with Mecholyl Chloride. GEORGE S. HUSSON * and CHARLES DICOSIMO,* State Univ. of N. Y., Syracuse (Introduced by Julius B. Richmond)

Severe recurrent paroxysmal supraventricular tachycardia presents a difficult problem in management in pediatric patients.

Digitalis has been reported in the literature to be of value. Other drugs such as quinidine, Prostigmin, etc. also have been used. Although the use of Mecholyl has been described in the treatment of this disorder, there has been almost universal condemnation of this drug because of the extreme danger attending its use.

Our experience in the treatment of an infant with recurrent paroxysmal tachycardia which failed to respond to adequate doses of digitalis and quinidine indicates that Mecholyl in appropriate dosage can be of considerable value. In addition, we have found that repeated use of Mecholyl did not produce serious reactions.

Lipton and others have determined experimentally on a physiological basis optimum doses of parasympathomimetic drugs for infants and children. The therapeutic doses of Mecholyl recommended are much lower than those previously employed in pediatric practice and were used by us. The course of a 2-month-old infant with 15-20 attacks of paroxysmal tachycardia who failed to respond to adequate doses of digitalis and quinidine and who was successfully treated with Mecholyl chloride in a maximum dosage range of 0.2-0.3 mg/kg. body weight will be discussed.

Conclusion.—The use of Mecholyl chloride in appropriate dosage has a definite place in the management of supraventricular paroxysmal tachycardia.

Lysozyme Levels in Cystic Fibrosis of the Pancreas. MORRIS N. GREEN,* SHEILA BLOOM,* and HARRY SHWACHMAN, Harvard.

Lysozyme is normally present in many body fluids (tears, sputum, etc.) where it exerts a protective effect against infection by its lytic action against many types of bacteria. Lysozyme disrupts bacteria because many organisms contain certain mucopolysaccharides in their cell wall which are hydrolysed by the enzyme. In a series of unpublished observations from this laboratory, Dr. Isaac Djerosi has observed that egg lysozyme reduces the viscosity of bronchial and nasal mucus. Elevated levels can be observed in the intestinal contents as the result of the leucocytic proliferation which accompanies ulcerative colitis. These observations prompted us to examine various fluids from patients with cystic fibrosis of the pancreas for their lysozyme content.

It was found that the duodenal fluid of patients with cystic fibrosis had a high level of lysozyme

as compared to the control group. In the control group of 63 patients the average lysozyme value was 3.5 gamma/ml.; in 32 patients with cystic fibrosis having complete pancreatic insufficiency the average value was 91.9 gamma/ml.; in 4 patients with partial or no pancreatic insufficiency the average value was 5.8 gamma/ml. When normal duodenal fluid was mixed with fluid from patients containing lysozyme under controlled conditions, the lysozyme was destroyed.

Experiments are now in progress, in an attempt to trace the source of lysozyme in doudenal fluid in patients with cystic fibrosis. Preliminary results show that patients with cystic fibrosis have higher lysozyme levels in gastic juice than normals. When normal gastic juice and saliva are mixed under controlled conditions, the normal fluid destroys the lysozyme from the saliva.

In another group of experiments, lysozyme levels from meconia were examined. In no case (10 specimens) could lysozyme be detected in normal meconia, while the meconia from three patients with meconium ileus showed lysozyme with an average of 63 gamma/gm.

The significance of these findings will be discussed.

Congenital Auriculo-Ventricular Block: A Clinical and Physiological Study. ABRAHAM M. RUDOLPH,* MILTON H. PAUL,* ALEXANDER S. NADAS, Harvard.

Congenital heart block has been encountered in 23 children, aged 1 day to 14 years. Two patients were asymptomatic and showed no evidences of heart disease, other than the heart block. Two additional patients had cyanotic congenital heart disease.

The remaining 19 patients presented a fairly homogeneous clinical, radiological and electrocardiographical picture. The characterizing clinical features were variable intensity of the first sound and systolic and mid-diastolic murmurs along the left sternal border. Radiologically they had generalized cardiomegaly, prominent main pulmonary artery, and increased pulmonary vasculature. Electrocardiograms revealed an auriculo-ventricular block, but otherwise no significant changes.

Five of the group have been studied by means of cardiac catheterization. These patients were thought on clinical grounds to have a ventricular septal defect and/or pulmonary stenosis. In two of these a left-to-right shunt at the atrial level was demonstrated. The other three patients showed no left-to-right shunt.

The hemodynamic changes associated with auriculo-ventricular block and slow heart rate will be discussed with particular attention to their role in the production of heart murmurs and cardiomegaly.

Agglutinability of Erythrocytes of Cord Blood in Colloidal Media: Relationship to A and B Incompatibility. VICTOR C. VAUGHAN III, Temple.

Examination of several hundred specimens of umbilical cord blood has indicated that the red blood cells show some degree of agglutinability in colloidal media (serum, glue, or acacia) in 10%-15% of instances. It has been demonstrated that this aglutinability, even when weakly present, bears a close relationship to A or B incompatibility between mother and infant. The occurrence in compatible infants of such agglutinability needs further study. It can be inferred, however, from the data to be presented that as many as 5% of newborn infants (20% of A or B incompatible infants) may have some laboratory manifestation of isoimmunization with respect to A or B; of these only about one-fifth have any clinical manifestation thereof.

The Pathology of the Liver in Cystic Fibrosis of the Pancreas. JOHN M. CRAIG, HESKEL HADDAD,* and HARRY SHWACHMAN, Harvard.

The gross and microscopic findings of the liver in 198 autopsied cases of cystic fibrosis of the pancreas were reviewed. The increasing age of autopsied patients with this disease and the changes in therapy over the years from 1920-1955 gave a nonhomogeneous picture. The most frequent finding was that of fatty infiltration, occurring in 130 patients. Periportal fibrosis was found in 45 cases but in 27 of these it was associated with hyperplasia of the bile ducts. The latter lesion gave rise to a focal biliary cirrhosis in 10 instances and a diffuse biliary cirrhosis in 8. Periportal fibrosis alone was never sufficiently extreme to be labeled cirrhosis. In no instance did the biliary cirrhosis lead either to liver failure or to clinical portal hypertension. Alterations in liver cell architecture were found in one third of the cases and these consisted of shrinkage, hemosiderosis, bile stasis and necrobiosis. Congestion was a finding in 80 cases but only rarely could it be ascribed to right-sided heart failure. Periportal and sinusoidal inflammation were found in 27 and 11 instances respectively. The significance of the lesions will be discussed in relation to therapy, age of the patients, and general nutritional status at the time of death.

Self-Regulatory Feeding in a Premature Infant Nursery: Observations on Caloric Intake and Growth in Weight. L. O. LUBCHENCO,* and R. Y. TING,* Colorado. (Introduced by John A. Lichty)

Data on caloric intake and growth have been studied in two groups of small premature infants (72 babies weighing 1500 gm. or less at birth). Caloric intake and growth in weight have been

computed for each week after birth for 11-12 weeks of life. One group was fed a regulated diet according to usual nursery practices in 1950. The babies in the other group were fed "on demand." In the group of premature infants fed amounts according to their hunger, an increasing caloric intake with each week of age was apparent. The median intake reached 120 cal/kg/day at 3 to 4 weeks of age. By 8 weeks of age it was 155 and at 11 weeks of age, 170 cal/kg/day. Incomplete caloric intake data gathered on this group of infants, to 6 months of age, still show a higher caloric intake than the full-term infants studied by the Child Research Council. The reasons for this large intake have not been determined.

The effect on caloric intake of nursery practices, birth weight, gestational age, age after birth and type of feeding mixture has been studied. Similar correlation with growth in weight was found in relation to birth weight, gestational age, and age after birth.

When caloric intake and growth in weight were compared with each other, some discrepancies were noted. Depending upon methods of analyzing data, comparing caloric intake and growth in weight, differing conclusions could be reached. For example, when relative growth (gm/kg/day) was compared with caloric intake (cal/kg/day), 110 cal/kg/day gave maximum gain. If actual gain in grams per week was compared with cal/kg/day intake, 140 cal/kg. gave maximum gain.

The data suggest that if an infant was given a diet which provided something more than a minimum of food, adequate growth occurred. Much greater amounts apparently had no effect in increasing the rate of gain in weight. The variations in the utilization of ingested food are currently being investigated.

Chemical Reorganization of Human Skin and Skeletal Muscle During Growth. JORGE MARTNER,* JACK METCOFF, IRENA ANTONOWICZ,* and WILLIAM RICHARDSON,* Harvard.

Variations in total body content of water or electrolytes, as estimated by isotope dilution or balance measurement, should be appropriately reflected in major organ systems such as skin and muscle. Each of these systems serves different functions in the chemical economy of the body, and a few recorded observations suggested that they undergo chemical reorganization with growth. Systematic assessment of the water and electrolyte composition of human skin and muscle during growth was needed to serve as a reference for interpretation of compositional changes in disease.

Biopsies of skin, subcutaneous tissue and muscle and blood specimens were obtained during various operative procedures on 24 children, 2 days to 10 years of age, who had no evidence of water or electrolyte imbalance. Samples also were obtained from two neonates immediately post-mortem.

In skin expanded extra- and intracellular water phases were consistent with edema of the neonatal period. No chloride "excess" was noted in addition to that contained in the "free" extracellular fluid when cell potassium concentration was used as basis for calculation. The potassium content, and presumably viable cell mass of neonatal skin was proportionately much greater than observed in older children. "Normal" skin composition was attained by one year of age. The Na/Cl ratio in skin gradually decreased from 1.32 at birth to 1.18 by 4-8 years of age. In the latter group the skin Na/Cl ratio was less than that of extracellular fluid.

In muscle the extracellular phase was isoosmotically expanded in the neonatal period, and the diminished intracellular phase contained more sodium and less potassium than characterize muscle from older children or adults. The sum of sodium plus potassium concentration of the intracellular water also was less than that observed in older children. The extracellular phase of muscle decreased exponentially with advancing age, and potassium content of the cell increased. Mature muscle composition was established by one year of age.

In the newborn infant, skin contains about 23% of total body chloride and 25% of the available extracellular fluid. About 40-50% of the body potassium and 20% of cell water are contained in muscle. In the older child, about 30% of the chloride and extracellular fluid are contained in skin, and approximately 75% of body potassium and about 40-50% of cell water are contained in the total muscle mass.

The observed extracellular edema of newborn infants with diminished intracellular volume and potassium concentration in muscle emphasize the hazards of acute disturbances in water and electrolyte balance in this age group relative to older infants or children.

Defects in Potassium and Water Metabolism in Cystine Storage Disease. F. FELLERS,* J. MARTNER,* H. RING,* K. SATJADIBRATA,* D. HSIA, J. CRAIG, and J. METCOFF, Harvard.

Cystine storage disease (Lignac-Franconi Syndrome) is a rare disorder of aminoacid metabolism of unknown etiology, but characterized by deposition of cystine crystals in tissue, and, after 2-3 years of age, failure of growth, hypokaliemia, hypotonicity of the extracellular fluids, aminoaciduria, polyuria, polydipsia, and ultimately death from renal insufficiency. An attempt to define some of the interrelationships characterizing disorders of cellular metabolism such as electrolyte composition of cells and renal regulation of their extracellular environment prompted investigations of this disease

in four affected children, two of whom were siblings. Three of these patients are living.

Balance measurements, electrolyte loading and depletion studies, renal tubular responses to these, and muscle and kidney biopsies to determine cell composition were employed.

Although the responses of each patient to the various challenges differed somewhat, inability of renal tubular cells to conserve body potassium when intake was acutely limited was demonstrated. In one instance removal of potassium by active tubular secretion in the absence of sodium or potassium loading was observed. Capacities for renal secretion of hydrogen ion with acidification of the urine usually were limited. Although excessive quantities of particular amino acids appeared in the urine, alpha amino nitrogen clearances measured in one patient were not remarkable and were independent of tubular potassium secretion.

Renal reabsorption of water appeared to be defective in this syndrome. Distal tubular water reabsorption apparently was governed by factors other than ADH activity, as the renal tubular cells were shown to have little or no response to parenteral pitressin. Since urine osmolality usually was less than that of the hypotonic serum, this type of "nephrogenic" diabetes insipidus may represent an ineffective renal defense of extracellular concentration.

Muscle cells were potassium depleted, but the loss of potassium did not necessarily exceed that of non-collagenous nitrogen (NCN), since a normal K/NCN ratio was maintained in one of the instances where measured. Intracellular sodium did not accumulate in amounts sufficient to replace depleted cell potassium and the children did not evidence significant extracellular alkalosis. Observations on the cationic amino-acid composition of muscle cells are in progress.

The defect of intermediary amino-acid metabolism apparently leads to accumulation of cystine in tissue cells with gradual alteration in the fundamental capacity of the cells to assimilate nitrogen and to retain potassium. Cellular potassium and protein depletion limit growth, presumably predispose to hypotonicity and polyuria, and may be factors in development of the renal lesions which ultimately prove fatal.

The Influence of the Liver on the Alterations in Renal Dynamics Produced by Intravenous Administration of Lysed Red Cells. WILLIAM J. A. DEMARIA and JEROME S. HARRIS, Duke.

A previous report demonstrated that intravenous infusion of lysed and partly clarified homologous red cells depresses the renal clearances of inulin and PAH in the dog. Immediately following cessation of the infusion, the GFR and ERPF returned to control levels despite the continued presence of a high level of circulating hemoglobin. Further, the change in renal dynamics seemed to vary with the rate of increase in plasma hemoglobin concentration rather than the ultimate level achieved.

To clarify these puzzling features, a group of experiments has been completed in which the hemoglobin solution was infused directly into the portal vein. No significant effect on the renal dynamics was noted although the rate of infusion and levels of circulating hemoglobin achieved were the same or greater than those in the peripheral infusion groups. To control possible individual variability among dogs as a cause of this result, other types of experiments were performed. After control clearances were completed, hemoglobin solutions were alternately infused into a peripheral vein and the portal vein. Again, significant reduction in renal clearances was recorded during the peripheral vein infusion and insignificant changes during the portal vein infusion. Whether these results can be explained by an alteration of the hemoglobin by the liver or by hepatic "detoxification" of other substances in the lysed red cells is now under investigation.

The Effect of Age on the Chloride Concentration of Saliva. JOSEPH DANCIS, EVELYN GROBOW,* and AUDREY BOYER,* N. Y. U.—Bellevue Medical Center.

The chloride concentration of saliva tends to be high in cystic fibrosis of the pancreas. In these patients, the Staphylococcus is a frequent inhabitant of the nose and throat. Since the Staphylococcus is also found frequently in the nose and throat of infants in the nursery, it was decided to investigate the chloride concentration of their saliva.

Twenty-eight infants varying in age from 1 day to 8 weeks were studied. The chloride concentration of the saliva was high during the first few days (26-82 mEq/L, average 56) and fell by the end of the week to the range of 20-35 mEq/L. The fall continues at a slow rate so that by the end of two years practically all determinations are 20 mEq/L or less. The precipitous drop postpartum was found in both premature and term infants indicating that this adjustment is related to birth rather than maturation.

The importance of these normal age variations in evaluating children suspected of cystic fibrosis of the pancreas is apparent. The effect of age on the chloride concentration of sweat is under investigation.

The Striopallidal Electrogram of Children with Extrapyramidal and Convulsive Disorders. H. W. BAIRD III,* H. T. WYCIS,* and E. A. SPIEGEL,* Temple. (Introduced by James B. Arey)

The insertion of electrodes into the human brain by means of a guiding apparatus (the

stereoencephalotome) described by Spiegel and Wycis permits exact placement of electrodes into subcortical structures. Recording electrodes can remain in the caudate nucleus, putamen, globus pallidus, or other nuclei for several days. These areas are determined preoperatively by air encephalograms which reveal the position of the foramen of Monro and of the anterior commissure in relation to the guiding apparatus. The present stereoencephalotome can be replaced one or more times in exactly the same position weeks or months later, so that circumscribed electrolytic lesions can be produced in areas where pathologic discharges have been detected.

Electrograms of the striatum (caudate nucleus, putamen) and pallidum have been obtained from five children simultaneously with the routine scalp EEGs. In addition to spontaneous discharges, the effect of certain tranquillizing and relaxing drugs was studied in each child. These agents included mebrobamate (Miltown, Wallace), chlorpromazine (Thorazine, SKF), reserpine (Rau-Sed, Squibb), zoxazolamine (Flexin, McNeil), bulbocapnine hydrochloride, and various barbiturates. Focal abnormalities in the activity of the basal ganglia may become manifest only under the action of some of these drugs. If such abnormalities are found occurring either spontaneously or only after the administration of certain drugs, they may serve as an indication for possible surgical intervention.

In four children, circumscribed electrolytic lesions of the pallidum and/or ansa lenticularis were made following the demonstration of focal abnormal electrical discharges. Three children definitely improved following the procedure. Their clinical diagnoses prior to surgery were dystonia musculorum deformans, tuberous sclerosis with mental retardation and uncontrolled convulsions, and spastic quadiplegia with athetosis. The child who did not improve had clinical evidence of a severe psychosis, probably secondary to a degenerative disease of the central nervous system.

One child in whom no electrolytic lesion was made was studied because of uncontrolled major and minor seizures. He was found to have diffuse abnormal electrical discharges which possibly originated in multiple foci.

Studies such as these may be useful in disorders of the so-called extrapyramidal system, particularly in patients with some types of chorea and athetosis and in certain convulsive disorders. In the latter patients, the subcortical electrograms may reveal much more definite seizure discharges than do scalp electroencephalograms. Such findings may help to localize a subcortical epileptogenic focus, the removal of which may beneficially influence the clinical course of the disease.

Detection of the Heterozygote in Phenylketonuria. DAVID YI-YUNG HSIA and KATHLEEN DRISCOLL,* Harvard.

Phenylketonuria is a hereditary disease characterized by severe mental retardation and the excretion of phenylpyruvic acid in the urine. The condition is transmitted as a simple recessive and occurs as a result of a deficiency in the enzyme system which converts phenylalanine to tyrosine.

If it is assumed that every gene has a measurable effect if it could be detected, it is worth while to seek the manifestations in heterozygotes of genes which are fully expressed only in homozygotes. Both parents of any homozygote must be heterozygous for the particular gene in question and those individuals would be the most likely ones to study for manifestations in the carrier. The following studies were, therefore, undertaken on the parents of patients with phenylketonuria and on normal controls: (1) presence of phenylpyruvic acid in the urine. This was done using a number of different chemical methods, both while in a fasting state and after the ingestion of 5 gm. of L-phenylalanine; (2) presence in the urine of p-hydroxy phenylpyruvate, p-hydroxy benzaldehyde, and other metabolites of the aromatic acid group by paper chromatography; and (3) plasma phenylalanine levels both in the fasting state and while on a normal diet. No detectable differences could be demonstrated by these tests.

It was decided, therefore, to place maximum stress on the enzyme system by undertaking phenylalanine tolerance tests; 0.1 gm. per kg. of L-phenylalanine was given by mouth after an overnight fast. Samples of blood were taken before, and one, two, and four hours after ingestion of the phenylalanine. The plasma phenylalanine levels were determined by a modification of the phenylethylamine method described by Udenfriend and Cooper. The heterozygotes showed both higher and more persistent elevations of phenylalanine levels as compared with the normal controls.

The clinical, genetic, and biochemical implications of detecting the heterozygote in phenylketonuria will be discussed.

Incidence of Infection with Poliovirus Among Personnel Caring for Patients with Acute Poliomyelitis. JOHN H. ARNOLD* and SIDNEY KIBRICK,* Harvard. (Introduced by Charles Janeway)

The purpose of this investigation was to determine the incidence of infection with poliovirus among a group of medical and nursing personnel caring for patients with acute poliomyelitis during the course of a severe epidemic. At the beginning of the study, specimens of serum were obtained from each of the participants and again after one month. Feces and pharyngeal swabs were collected at weekly intervals from most of the

persons included. Sera were tested for the presence of neutralizing antibodies against the three types of poliovirus. The other materials were examined for the presence of virus by appropriate tissue culture techniques. The results will be presented.

Cortisone Protection from Reversed Anaphylaxis. DOUGLAS E. JOHNSTONE, Rochester.

A rabbit antiserum, suitable for producing reversed anaphylaxis in guinea pigs, was prepared by giving repeated intravenous injections of normal guinea pig serum to healthy young adult albino rabbits. After a suitable interval the rabbits were bled and the antiserum tested for its anti-guinea pig serum antibodies. These antibodies were demonstrated in vitro by a precipitin technique. They were demonstrated in vivo by the production of immediate fatal reversed anaphylaxis after intravenous injection in guinea pigs and by antibody-neutralization tests in guinea pigs. Normal rabbit serum was shown incapable of giving similar in vitro and in vivo results.

After proving the potency of this rabbit serum, attempts to produce reversed anaphylaxis were made in (1) guinea pigs who had received an $L.D._{50}$ dose of whole body ionizing radiation, (2) guinea pigs who had received varying amounts of cortisone intramuscularly or intraperitoneally, (3) irradiated guinea pigs who had received varying amounts of cortisone, and (4) irradiated guinea pigs who had received intramuscular injections of ACTH prior to challenge with the antiserum containing the anti-guinea pig serum antibodies. The accompanying table lists the results.

Group	Total No. of Animals	No. showing shock and death	No. recovering after challenging injection
Controls	63	56 (88%)	7 (11%)
Irradiated guinea pigs	19	16 (84%)	3 (15.8%)
Irradiated guinea pigs treated with cortisone	37	34 (92%)	3 (8%)
ACTH-treated guinea pigs (irradiated)	25	10 (40%)	15 (60%)
Non-irradiated guinea pigs treated with cortisone	114	52 (45%)	62 (54%)

In addition data will be shown to demonstrate that in nonirradiated guinea pigs, the dose and time of administration of cortisone markedly influence the survival rate in this experiment.

The significance of these data will be discussed.

Studies on the Influence of Whole Body Ionizing Irradiation Compared to Localized Superficial Beta Irradiation on the Shwartzman Phenomenon. DOUGLAS E. JOHNSTONE, Rochester.

The effects of an $L.D._{50}$ whole body exposure to X-ray irradiation on susceptibility to the elicitation of the Shwartzman reaction was studied on 65 albino rabbits. Attempts to elicit this phenomenon in rabbits were made at varying intervals after irradiation. Daily blood counts were made in each rabbit to test the validity of the contention that leucopenia renders animals incapable of producing a localized Shwartzman reaction. To this end, attempts were made to produce this reaction in rabbits rendered leucopenic by nitrogen mustard infusions in 36 rabbits. Although leucopenia induced by nitrogen mustard infusions did inhibit the elicitation of a localized Shwartzman reaction, leucopenia induced by whole body irradiation did not inhibit the production of this phenomenon. Microscopic sections of representative members of these two groups will be shown. The differences in these two groups in regard to reversal of acquired resistance to the Shwartzman reaction after intravenous infusions of colloidal carbon will also be presented.

The effect of superficial beta irradiation from a strontium^{90}-coated applicator on this skin reaction was studied in 15 rabbits. At varying intervals after exposure, attempts to elicit a localized Shwartzman reaction were made at the locally superficially irradiated skin sites as well as at control, nonirradiated sites in the same animals were made. The differences in the skin reaction in the two sites will be shown.

The results of this study suggest that a reappraisal of previous knowledge of the mechanism of this reaction is demanded.

Portal Venography: An Aid to the Differential Diagnosis and Management of Portal Hypertension in Children. A. SASS-KORTSAK, J. D. MUNN,* and CODE SMITH,* Toronto.

Proper management of patients suffering from portal hypertension necessitates the determination of the site of obstruction to portal blood flow. Angiography is widely used with success to detect pathological aberrations in different parts of the vascular system. The portal venous channels are difficult to reach with this method due to their unique property of being situated in the abdominal cavity between two capillary beds. Injection of

radiopaque substances into a tributary of the portal system after opening of the abdomen and preceding the shunting procedure has been used, but prolongs the operation and may not leave time for careful evaluation of the findings. Moreover, the use of rapid film changing apparatus in the operating room is impractical.

The discovery by Abbiatici and Campi of the fast entry of the rapidly injected radiopaque dye from the splenic pulp into the splenic vein and thence into the portal venous system opened up the possibility of obtaining satisfactory portal venograms via a needle inserted into the spleen through the skin. Their method has been successfully used by Sherlock, Blalock, Leger, Budtz-Olsen, and others, mainly in adults.

An attempt was made to explore the possibilities offered by this method in the pediatric age group. Under short general anaesthesia aided by the use of a muscle relaxant, transcutaneous splenic portography was performed on 12 children and infants suffering from portal hypertension and sequelae. In this relatively small series no accidents occurred and no untoward effects are observed, except transient abdominal pain. The technique employed will be discussed in detail.

Of the 12 patients 5 suffered from chronic liver disease with secondary portal hypertension, 5 had extrahepatic obstruction to portal blood flow, one was proved by the procedure to have no portal hypertension, and one was unsuccessful.

The value of the procedure will be illustrated by demonstration of the x-rays obtained. In some of these cases useful added information was obtained by the simultaneous measurement of intrasplenic and vedged hepatic vein pressures.

Sequential Alterations of Serum Lipids in Different Types of Obstructive Jaundice in Early Infancy. A. SASS-KORTSAK, O. V. SIREK,* and N. T. JACO,* Toronto.

The liver plays an important role in lipid metabolism and alterations in the concentration of serum lipids are known to exist in different types of liver disease. It appears from the available data that intra- or extrahepatic obstruction to the biliary flow, with slight or no changes in the liver parenchyma, is associated with an elevation of serum lipid levels. On the other hand the serum lipids and particularly the esterified fraction of cholesterol are low in the presence of marked parenchymal damage.

In the present study an attempt has been made to learn more about the nature of the pathological process and to provide help in the differential diagnosis of regurgitation jaundice in early infancy by investigating sequential changes in serum lipid levels.

The following groups of patients were studied:
(1) congenital extrahepatic biliary atresia
(2) intrahepatic biliary atresia
(3) inspissated bile syndrome complicating hemolytic disease of the newborn
(4) "neonatal hepatitis"

Total number of patients—20.

Total fat, lipid phosphorus, and cholesterol (total and free) estimations were carried out in duplicate on 1.5 ml. of serum. The level of "neutral fat" was calculated from the above data. Other liver function tests, such as serum bilirubin estimation, serum protein fractionation, cephalin cholesterol flocculation, thymol turbidity and flocculation, measurements of alkaline phosphatase and serum cholinesterase activity, were carried out on the same blood specimens.

The three patients suffering from intrahepatic atresia of the bile ducts showed the most marked changes in serum lipids. The levels of all the serum lipid fractions were unusually high, total fat from 2000-4000 mg.%, phospholipids and total cholesterol close to or over 1000 mg.%. The calculated amounts of "neutral fat" in the serum were also far above the normal level. None of the patients in the remaining groups showed such abnormally high figures.

The patients suffering from congenital extrahepatic biliary atresia had elevated serum cholesterol levels in the first half year of their life; these levels gradually decreased with the progressive development of biliary cirrhosis.

The results were more variable in the group of obstructive jaundice complicating hemolytic disease. Some cases showed no change, others had moderately elevated serum cholesterol and phospholipid levels.

The five cases of "neonatal hepatitis" had normal or only slightly elevated serum lipids in the first few months of their disease. The percentage of esterified cholesterol was decreased in the more severely affected patients.

The significance of these findings and their correlation with the other liver function tests will be discussed in detail.

Recently efforts are being made to characterize the lipoprotein pattern in these patients by ultracentrifugal flotation at four different densities. The results obtained in a patient with intrahepatic biliary atresia shall be demonstrated.

The Effect of Whole Blood Compared with Sedimented Red Cells in Exchange Transfusions. THOMAS R. C. SISSON,* Rochester. (Introduced by Gerald Miller)

A comparison was made of certain effects on exchange transfusion of whole blood preserved in A-C-D versus sedimented red cells. Two groups of six infants with hemolytic disease of the newborn due to Rh incompatibility were studied. This

evaluation was based on blood volume studies (using T-1824) done immediately prior to exchange transfusion and 24 hours later. The effect of the two types of donor blood, whole and sedimented, on serum bilirubin rise following transfusion was also observed.

Data for comparison include: hemoglobin concentration, venous hematocrit, serum bilirubin, plasma volume, blood volume, red cell volume, and circulating hemoglobin mass.

All transfusions were done through the umbilical vein, and according to the nomogram of Mollison and Veall. The studies were performed on infants transfused in the first or second day of life. The birth weights of all infants were between 2940 and 3930 grams. The degree of anemia as judged by the initial hemoglobin concentration and hematocrit was comparable in the two groups (with the exception of two infants more severely anemic). Severity of the disease was moderate in each case, and the need for exchange transfusion, by the accepted criteria, placed these infants in a common group. The infants were not specially selected for treatment by either type of replacement transfusion.

Analysis of studies made 24 hours after transfusion of sedimented cells showed that the hemoglobin concentration and hematocrit increased 4.0 gm/100 ml. and 7.8%, respectively. The plasma volume decreased 9.5 ml/kg., the blood volume decreased 3.1 ml/kg., and the red cell volume increased 6.2 ml/kg. The total circulating hemoglobin mass increased 3.8 gm/kg.

In contrast, when whole blood was used, hemoglobin concentration decreased 0.4 gm/100 ml., and hematocrit decreased 5.4%. The plasma volume increased 0.6 ml/kg., blood volume decreased 4.0 ml/kg., and red cell volume decreased 4.1 ml/kg. The circulating hemoglobin mass decreased 0.8 gm/kg.

It was found that the rise in serum bilirubin, subsequent to exchange transfusion, differed in the two groups. The infants who received whole blood demonstrated a serum bilirubin rise above 20 mg.% in 7 of 10 transfusions, and this concentration was exceeded in 5 of the transfusions within 36 hours. The bilirubin rise in the group that received sedimented cells exceeded 20 mg.% in only 3 of 10 transfusions, and this within 36 hours.

These results lead to the conclusion that sedimented cells do not produce a deficit of total circulating hemoglobin and red cell volume in exchange transfusion, as does whole blood.

The effect of whole blood compared with sedimented cells on the serum bilirubin rise following exchange transfusion will be discussed.

Prevention and Treatment of Streptococcal Disease with Penicillin V. PAUL F. WEHRLE* and HARRY A. FELDMAN, State University of New York, Syracuse.

As compared with penicillin G, phenoxymethylpenicillin (penicillin V) would appear to have a pharmacological advantage in that higher and more prolonged levels are obtained after oral administration. This difference may be particularly important in the elimination of the streptococcal carrier state with relatively small single daily doses of penicillin. In addition, effective treatment of the acute case of streptococcal disease may be accomplished with smaller oral doses of penicillin than are commonly employed, provided penicillin V is utilized.

The present study consists of an evaluation of the comparative response of Group A hemolytic streptococcal carriers to penicillins V and G. A single dose of 200,000 U. of V or 250,000 U. of G was given daily before breakfast over a 10-day period to a total of 118 children. Sixty-three children received V while fifty-five received penicillin G. The two groups of children lived in separate portions of a single institution and were treated simultaneously.

Initial and several subsequent throat cultures were obtained to determine the comparative response to the penicillins. Data regarding persistence of the carrier state and the occurrence of minor illness and streptococcal disease will be presented.

In addition to the data on carriers, some information is also available regarding the treatment of streptococcal pharyngitis and scarlet fever with penicillin V, using oral doses of 200,000 units three times daily. The bacteriological and serological response as measured by antistreptolysin O titers are included.

Some Epidemiologic and Control Aspects of Two School Streptococcal Epidemics. HARRY A. FELDMAN, DAVID C. POSKANZER,* and WILLIAM G. BEADENKOPF,* State University of New York, Syracuse, and N. Y. State Health Dept.

During recent epidemics of acute streptococcal disease in two upstate New York communities it was possible for us to study various aspects of their epidemiology and control. The two communities are in rural areas several miles apart, but the streptococcal types involved were somewhat different in that types 1 and 6 predominated in one epidemic, but Type 3 predominated in the other; some Type 6 was isolated from this one as well. A sample of the approximately 500 children, school teachers and bus drivers concerned with the central school in the one town were studied by means of throat cultures. All students, administrative personnel, teachers, and bus drivers then were given

250,000 units of Penicillin G by mouth, twice daily for 10 consecutive days. The drug was administered by the classroom teachers. Permission to do this was obtained from almost all parents. Those children who had histories of sensitivity to penicillin received tetracycline, 250 mg. twice daily for 10 days. Follow-up cultures were performed at several intervals thereafter. Control of the epidemic was prompt and the streptococcal rate has not returned to any significant level during several weeks of follow-up. Although the over-all incidence of positive cultures was very high, the frequency with which streptococci were detected among the kindergarten and first four elementary grade pupils was considerably greater than among the remainder of the school.

In the second community, a representative sample of the student body, administrative personnel, bus drivers, and school teachers was cultured prior to beginning treatment with one tablet of 250,000 units of Penicillin G daily on each of 10 consecutive days. The drug, again, was distributed by the classroom teachers. The response was neither as complete nor as persistent as had been noted in the community in which twice this dose had been used. In addition, a culture study was conducted among the families of approximately 65 children included in the school sample, both prior to the institution of mass prophylaxis and following the completion of treatment among the school children. The streptococcal types encountered among these family contacts will be discussed in detail.

Increased Urinary Gonadotropin (FSH) in an Infant with a Functioning Ovarian Tumor. JOHN F. CRIGLER JR. and EDNA H. SOBEL, Harvard.

An 11-month-old Italian girl was admitted to the hospital with breast development, pubic hair, enlarged labia minora, enlarged clitoris, and increased pigmentation of areolae and genitalia. A firm mass filled the entire right abdomen and its lower portion extended into the left abdomen. X-ray studies excluded the possibility of a suprarenal mass. Bone age was 18 months. The vaginal smear showed definite estrogen effect. At operation, a one-kilogram right ovarian tumor was removed which histologically was a mesenchymoma consisting of poorly differentiated granulosa and theca cells with much pleomorphism and numerous mitotic figures.

Hormonal studies preoperatively revealed urinary 17-ketosteroids of 0.7 mg/24 hours, urinary estrogens of 14 and 20 micrograms/24 hours, negative A-Z test and an FSH assay strongly positive at 2.5 mouse units. The FSH was not determined at higher dilutions at this time. Except for the elevated FSH, these values were normal for her age.

Postoperatively, the patient did exceedingly well with complete regression of her precocious development. Seven months after operation, urinary 17-ketosteroids were unchanged and the FSH remained positive.

As a rule, a positive gonadotropin assay in a prematurely developed girl is thought to establish the diagnosis of true sexual precocity. In the presence of a readily palpable abdominal mass the diagnosis of pseudo-precocity is made and the gonadotropins have not usually been measured. The significance of the positive gonadotropin in this patient is not clear. Since her precocity regressed postoperatively, it seems unlikely that the tumor occurred in the course of true sexual precocity. Two other possibilities are that the increased FSH is a result of pituitary activity elicited by the functioning overian tumor or that it preceded the development of the tumor and is, therefore important in ovarian tumor genesis. In this respect it is interesting to note that functional ovarian tumors are most common in post-menopausal women.

The Widespread Presence of Group B Coxsackie Viruses in the Gastrointestinal Tracts of Normal Children in an Orphanage. JUAN C. RIVADENEIRA,* MARIA A. CREA,* and FREDERICK C. ROBBINS, Western Reserve.

The study to be described here was initiated following the recognition in August, 1953, of two cases of clinical poliomyelitis among the 400 children of an orphanage.

The first child proved to be infected with Type 1 poliomyelitis virus. In retrospect it would appear reasonable to assume that his infection was acquired during a brief stay in the hospital on the Contagious Division two weeks prior to the onset of poliomyelitis. The second case was non paralytic and on laboratory investigation no evidence of poliomyelitis infection was found. However, Coxsackie B_4 was isolated from his stools.

Stool specimens from 153 of the 400 children whose ages ranged from 4 to 16 years were tested for virus in monkey kidney cell tissue cultures. Stool specimens from 43 of the 55 adult staff of the orphanage were also tested. Other than the two patients mentioned a few of the children in the institution suffered from various mild illnesses with fever and headache, but there was no undue prevalence of disease. There were no cases of herpangina or pleurodynia recognized. Twenty-four of the 153 normal children were found to have cytopathogenic agents in the stools. No agents were isolated from the adults. None of the cytopathogenic agents proved to be poliomyelitis viruses. Seven were typed as Coxsackie viruses; 4 were B_4 and 3, B_2. Two agents behaved differently in culture than the others and one of these failed to be neutralized by the available Coxsackie antisera that were A_9, B_1, B_2, B_3, and B_4. These two are

classified as unknowns or Echo viruses. The remaining 15 were not typed, but on the basis of their biological behavior are most likely Coxsackie B_3 or B_4. Poliomyelitis neutralizing antibodies of the three types were found to be present in a large portion of the children tested which may explain the failure of poliomyelitis virus to become disseminated in this population.

Neutralizing antibodies to Coxsackie viruses B_3 and B_4 were also present in the sera of the majority of 50 children tested and approximately 30% showed evidence of antibody rise over a period of from 5 to 6 weeks.

Outbreak of Enteric Fever Due to Salmonella Paratyphoid B: (1) Clinical and Laboratory Features in Hospitalized Patients; (2) Lack of Need for Massive Dosage of Chloramphenicol in Acute Disease. ROBERT H. PARROTT,* DAVID B. COURSIN,* HENRY G. CRAMBLETT,* LEWIS E. GIBSON,* and CHARLES H. KURTZ,* National Institute and St. Joseph's Hospital, Lancaster, Pa.

In an apparently milk-borne outbreak of enteric fever due to Salmonella paratyphoid B, there were 215 reported cases and over 70 hospitalized patients. A team of clinical investigators, by chart review and examination of 66 hospitalized patients, mostly children, learned the following:

(1) Fever, diarrhea with abdominal cramps, and rose spots were the major clinical features. Respiratory and suggestive neurological signs were relatively common. Fever lasted 10 days; rose spots started on the 7th day and lasted 6 days. Dehydration was not marked.

(2) Leukocyte counts were in general not significantly abnormal.

(3) Seventy-two per cent of those tested had a positive culture from some source: blood—72%; feces—65%.

(4) Significant antibody levels against specific flagellar antigen were present after the fifth day of illness in most patients. Less had antibody to Typhoid or paratyphoid B somatic antigens; some showed a fall in these antibodies by the tenth day.

(5) There was no significant difference in effect on acute illness of low or high chloramphenicol dosages.

Clinical Features of Infection with APC (Adenoidal-Pharyngeal-Conjunctival) Viruses (Pharyngo Conjunctival Fever). ROBERT H. PARROTT, M.D., National Institutes of Health.

APC viruses are very prevalent newly isolated tissue culture epitheliotropic agents. They have been found in (1) surgically removed tonsils and adenoids (types 1 through 6); (2) an illness for which the name pharyngoconjunctival fever is suggested (Type 3); (3) acute respiratory disease in military recruits (types 4 and 7); (4) febrile pharyngitis in children (types 1, 2, 3 and 5); (5) catarrhal conjunctivitis (types 6, and 10), (6) Epidemic keratoconjunctivitis (Type 8); (7) poliomyelitis survey (Type 10).

The clinical features of pharyngoconjunctival fever include the following:

Symptoms	Frequency
Fever	90%
Sore throat	70%
Red eyes	66%
Headache	68%
Malaise, weakness	72%
Signs	**Frequency**
Fever 102-104 for 4-5 days	90%
Pharyngitis	75%
Cervical adenopathy	75%
Posterior	66%
Rhinitis	50%
Conjunctivitis	75%
Unilateral	25%
Bilateral	50%

A Sex-Linked Genetic Syndrome in a Negro Family Manifested by Thrombocytopenia, Eczema, Bloody Diarrhea, Recurrent Infection, Anemia, and Epistaxis. JAMES A. WOLFF* and MARY BERTUCIO,* Columbia.

This is a report of a sex-linked recessive genetic syndrome affecting at least six male members of a Negro family, of which the case histories of two will be given in detail. The syndrome is characterized by a variety of findings of which thrombocytopenia, eczema, bloody diarrhea, recurrent infection, anemia and epistaxis are cardinal features. In 1954, Aldrich, Steinberg, and Campbell reported an apparently identical genetic condition in a white family. To our knowledge, no other instances of this syndrome have been reported.

One of our two patients is now 4½ and the other is 1½ years of age. Although thrombocytopenia and other manifestations of the disease have persisted, both children are now in reasonably good health. Of the other affected members of the family, four male children died by the age of 2½ years. There are several other male members of the family who are still alive who show some, but not all, of the features of the condition.

Clinical studies concerning the nature of this syndrome will be presented. Gamma-globulin levels have been normal. Although a resemblance to Letterer-Siwe's disease may be noted, the genetic pattern of the condition, as well as other factors, differentiate this condition from reticuloendotheliosis.

Studies on the Concept of Intracellular Osmotic Activity. WILLIAM TUTTLE,* WILLIAM A. BRODSKY, WARREN S. REHM,* and WARREN H. DENNIS,* Louisville.

If the observed hypertonicity of tissue homogenates is due to an explosive type of metabolism, active at 0 C, then maneuvers designed to stop the metabolic activity of freshly excised tissues might

provide an isotonic tissue preparation. Moreover, the osmotic activity of such a preparation would be stable with time in contrast to that of frozen pulverized tissue homogenates wherein the osmolarity increases with time.

Small pieces (Ca. 0.2 gm.) of liver and kidney were removed, without hemostasis from nembutalized dogs, and immersed immediately into tared breakers containing water at 90-100 C for 30 minutes. Freezing point determinations were made on the diluted extracts and on the heat-dried and reconstituted extracts of these tissues. The same procedure was performed on whole blood. In two of the first four experiments, liver osmolarity was equal to that of serum, 292 m0sm/L. Freezing point determinations of freshly excised, frozen tissue homogenates made from the same tissues were 340-350 m0sm/L. The value for boiled whole blood was 30 m0sm/L. less than that of serum in some experiments. The osmolarity of all boiled tissue extracts was stable with time. These data suggest but do not prove that cell fluid is isotonic to extracellular fluid.

If cell fluid is isotonic normally, then the hypertonicity of homogenates made in liquid N_2 could be due to the changes of tissue proteins induced by extreme cold and mechanical forces. Superficially, the observed isotonicity of some of our boiled extracts appears to be convincing evidence in support of the cellular isotonicity concept. Even though boiling changes protein characteristics and possibly tissue osmotic activity. It seems fortuitous that the change would render isotonic a tissue that had been hypertonic. The hypotonicity of boiled whole blood remains unexplained. Apparently, the concept of an iso-osmotic cell fluid is not established rigorously as yet, but the freezing point depression of some boiled tissue extracts is equal to that of plasma.

Bilirubin Levels in Premature Infants. JOHN M. BOWMAN,* GARRISON RAPMUND,* and R. C. HARRIS, Columbia.

Plasma bilirubin levels and hematocrit values, both determined on venous blood, were studied daily in 70 premature infants in the weight range 1000-2000 grams during the first week of life.

Of the infants studied, 14.7% showed peak bilirubin levels of over 20 mg. per 100 ml. (7.4% exceeding 25 mg. per 100 ml.). Conversely, 20.6% never reached 10 mg. per 100 ml. (6% remaining below 5 mg. per 100 ml.).

In our presentation these bilirubin levels will be correlated with the birth weight and clinical course. Postmortem findings in 13 of the 15 infants who died will be discussed. To date no proved case of kernicterus has been demonstrated in this group. This finding contrasts with the high incidence of kernicterus associated with peak bilirubin levels around 15 mg. per 100 ml. noted in a similar study done last year at Babies Hospital by MacLean, Lucey, and Harris. The marked increase in kernicterus in that series was confined to a group of infants receiving a prophylactic Gantrisin salt.

The absence of kernicterus in our patients with comparable bilirubin levels, who were given no Gantrisin, further substantiates the belief that administration of this Gantrisin salt may have a direct relation to the developmnet of kernicterus in premature infants.

Physiological Effects of Hypophysectomy and of Amphenone Administration in a Child with a Functioning Metastatic Adrenal Cortical Carcinoma. EDNA H. SOBEL, ALBERT E. RENOLD,* JOSEPH HOET,* JOHN E. BETHUNE,* and GEORGE W. THORN,* Harvard.

The patient was a girl, under our observation from age 7 7/12 until her death at 7 10/12 years. Surgical excision of an adrenal tumor, followed by irradiation of the tumor bed, was undertaken when she was 7 3/12, three months after the first manifestations of virilism. Althought the immediate response was gratifying, the tumor recurred, symptoms reappeared and pulmonary metastases became evident at 7 6/12.

At 7 7/12, she was virilized but had only slight manifestations of Cushing's syndrome and moderate hypertension (130/100). During the period of observation there was marked aggravation of the endocrine disorder, including progressive virilism and hypertension (to 200/120) and development of obvious Cushing's syndrome with glucosuria, moonface, and striae. Steroid excretion values (expressed per gm. creatinine excreted), paralleled the clinical picture and included: 17-ketosteroids from 70 to 150 mg. (normal, 2-5), 17-hydroxycorticoids from 20 to 85 mg. (normal 1-10) and markedly elevated aldosterone levels. Three major efforts to influence the course of the disease were made.

(1) Total hypophysectomy was performed at age 7 8/12, since some increase in steroid excretion followed the administration of corticotrophin and because of the possible stimulation of tumors by growth hormone. During the first week there was a fall in steroid excretion to less than one-half the preoperative levels, and the acne improved markedly. Thereafter, the disease advanced steadily. Diabetes insipidus and hypothyroidism were readily controlled. At postmortem examination at 7 10/12, in addition to extensive retroperitoneal and pulmonary tumor, a few anterior pituitary cells were found beneath the dura of the sella turcica. It is not clear whether the advance in tumor growth subsequent to the apparent improvement following hypophysectomy should be ascribed to this scant anterior pituitary remnant or to adaptation of the tumor to the new conditions.

(2) A course of oral and intravenous triethylene-thiophosphoramide (thio-TEPA) failed to influence the growth or function of the tumor.

(3) Amphenone (provided by Dr. Roy Hertz) was administered by mouth on two occasions, first at age 7 7/12 (before hypophysectomy for 4 days in amounts from 3 to 6 grams and again at age 7 10/12 for 16 days, in doses progressively increased from 4 to 12 grams. In each instance, there was a distinct reduction in the excretion of all the steroids listed, a complete disappearance of glucosuria, and dramatic improvement in the patient's physical appearance and hypertension. When Amphenone was discontinued at the end of the second course the steroid excretion rose to the highest levels observed in the patient's illness, suggesting that the compound might have served to block hormone release rather than as a carcinolytic agent.

The best chance for survival still resides in complete removal of malignant tissue following prompt diagnosis, which is made more readily when an endocrine tumor is functioning and hence calls attention to its presence.

Urinary Amino Acids in Wilson's Disease: A Family Study. Ruth C. Harris and I. Herbert Scheinberg,* Columbia.

Hepatolenticular degeneration, a disease of late childhood and adolescence, is characterized by clinical signs of brain or liver damage and by deficient serum ceruloplasmin levels, decreased total plasma copper levels with an increase in the directing-reacting fraction of the plasma copper, increase in tissue concentration of copper and increase in urinary copper excretion. Urinary excretion of amino acids is increased.

Much controversy has existed concerning the primary and secondary deficiencies of this disease. Family studies by Bearn and Kunkel point to abnormality of copper metabolism with amino-aciduria as an inconstant finding in patients with the clinical disease. Scheinberg and Gitlin believe that deficient ceruloplasmin production is the prime defect.

To evaluate the role of the amino-aciduria, urinary total amino acid excretion in six members of one family and chromatographic identification of individual amino acids have been studied. One 14-year-old member of this family has neurologic signs characteristic of hepatolenticular degeneration with increased number and total excretion of urinary amino acids. All other members, including a 13-month-old brother with a deficient ceruloplasmin blood level, have normal excretion of amino acids.

Prophylactic treatment of the infant will be discussed.

Clinical Effects of Phenylalanine Restrictive Diet in Phenylketonuria. James F. Bosma, Niels L. Low,* Marvin D. Armstrong,* Frank H. Tyler,* Jack A. Madsen,* John W. Carlisle,* Utah.

This report is concerned with study of six phenylketonuric patients who have received a total of 56 months of phenylalanine-diminished diet. The consistency and effectiveness of the selective dietary regimen was evaluated by determination of blood levels of phenylalanine. The patients have been the subject of periodic clinical observations, supplemented by 39 electroencephalograms, commonly employing sleep facilitation of seizure demonstration. As reported previously, the dietary regimen has been consistently effective in causing improvement of seizure disorder and of neurologic performance in one to three weeks following its initiation.

Comparison observations were made on 14 other older phenylpyruvic children, 2 of which were siblings of 2 of the test subjects.

A particular concern of this study is that of evaluation of optimal and effective duration of therapy. While under repetitive chemical, clinical, and electroencephalographic observations, dietary therapy has been replaced by normal diet in one subject at 10 months, after 7 weeks of dietary control, and in another subject at 15 months of age, after 7 months of dietary control. In each instance there were distinct evidences of neurological regression, and improvement again following resumption of therapy. Normal diet was later resumed in three subjects at 23, 28, and 48 months of age, after 10 to 22 months of dietary control.

In most children, the hypsarrhythmic seizure discharges disappeared from the electroencephalograms and did not recur after the phenylalanine-restricted diet was discontinued. One child, who is still on the diet, still has these seizure discharges.

The differential significance of effect of phenylalanine-restricted diet upon seizure and general neurological disability will be discussed. Consideration will also be given to the precautions of estimation of profits of this regimen upon the evolution of the more mature elements of mental performance.

The Growth of Continuously Growing Structures. Maarten Sibinga,* New York University. (Introduced by L. E. Holt Jr.)

In evaluating the day-to-day nutritional status of his patients the pediatrician has relied upon weight gain more than on any other criterion. The limitations of this criterion caused by fluid shifts, variations in food intake and in excreta are well known. Measurements of growth have definite advantages but it has not been possible to assay growth accurately over short periods of time.

The present report describes a method of measuring day-to-day growth with accuracy. It is a modification of the method devised by Babcock at Rutgers University for measuring the growth of a continuously growing structure—the finger nail. A photographic technique is employed, growth being measured by the distance between the lunula of the nail and a transverse scratch. When suitably enlarged this distance can be readily measured.

The method is applicable at all times of life. We have employed it in premature infants. That the growth of the nail reflects untoward nutritional influence is not new—it was demonstrated many years ago by Schick.

Rates of nail growth show well-defined individual variations. An attempt is being made to correlate these with susceptibility to various pathological processes. It is suggested that students of growth may be interested in including measurements of the growth of continuously growing structures in their longitudinal studies.

Mitochondrial Sub-Units Containing the Electron Transport System. J. L. Gamble Jr. and A. L. Lehninger,* Johns Hopkins.

Studies have been carried out of surviving enzyme systems in a preparation of mechanically fragmented mitochondria from rat liver. A small particle fraction has been isolated and has been found to retain a large portion of the electron transport activity. This activity has been characterized on the basis of oxygen uptake with eight substrates, and the data, presently available, appears to describe a unit of organization of a single type. Studies are continuing, using different tissues, in an atemtp to increase our understanding of the basic nature of these sub-units and of their relation to oxidative phosphorylation.

Sequelae of Prednisone Treatment of Acute Rheumatic Fever. Richard T. Smith,* Robert A. Good, and Sol J. Zak,* Minnesota.

Recent reports in the literature have suggested that permanent cardiac damage occurring during the course of acute rheumatic fever may be modified, or even prevented, by steroid hormone treatment, provided that large doses are employed and treatment is continued for 6-8 or more weeks. On the basis of these promising results, an experimental attempt was made to prevent cardiac sequelae. Eleven children having acute rheumatic fever were treated with large doses (up to 100 mg/M²/day) of prednisone for 40 to 171 days. Because of severe osteoporosis and compression fractures of vertebrae in three of the patients, the study was discontinued, the dose being reduced stepwise over a 3-4 week period.

During the early post-treatment period, "rebound," with elevation of the sedimentation rate, appearance of C-reactive protein, fever, but no rheumatic manifestations, occurred in 9 of the patients. In seven, "rebound" lasted 4-8 weeks. During this period, five of these children developed a peculiar syndrome lasting 4-14 days and characterized by intense pruritus, painful erythema nodosum-like lesions of the skin, and two developed extensive panniculitis. Biopsy material from the involved areas revealed fibrinoid occlusion of multiple venules, and striking subcutaneous fat necrosis.

Three children developed congestive heart failure, 25 and 60 and 90 days after cessation of therapy, without clinical evidence of recurrent rheumatic fever. One of these children died; at autopsy no evidence of recrudescent rheumatic carditis was evident, but fat necrosis and multiple vascular lesions, similar to that seen in the skin biopsies, were prominent. Clinical, photographic and histopathological data on these patients will be presented. Similar clinical and histopathological changes have recently been observed in a leukemic patient following prolonged prednisone therapy.

Preliminary results of various attempts to reproduce an analogous state of vulnerability in experimental animals indicate that 10 and 14 days after cessation of prolonged steroid therapy in rabbits, there exists a state of extreme susceptibility to Gram-negative bacterial endotoxins. These studies will be presented.

These observations, taken with other available evidence, permit the hypothesis that "rebound" after prolonged steroid therapy may reflect the introduction of a new disease process, possibly reflecting post-treatment vulnerability of small blood vessels, rather than a recrudescence of previously existing rheumatic fever.

Also, the observations indicate that the multitudinous physiologic and biologic effects of these hormones are still not fully understood, and illustrate the necessity for caution before advocating widespread use of large doses of steroids in treatment of acute rheumatic fever.

Iatrogenic Cellular Sodium Intoxication. G. A. Kerrigan,* J. D. Crawford, M. Terry,* and N. B. Talbot, Harvard.

Detailed metabolic balances conducted on four patients receiving parenteral fluids for diverse reasons, whose initial body potassium stores were essentially normal indicate defense of normal body composition whether sodium was given alone or given in company with potassium during the early hours of therapy.

In a second group of four patients who were potassium depleted at the start of therapy, balance data indicate that the administration of sodium unaccompanied by potassium or in excess of potassium by as little as 2.5:1 during the early hours of therapy, resulted in intracellular sodium intoxication and sustained metabolic alkalosis. These

changes were resistant for periods of several days to the subsequent provision of liberal quantities of potassium.

A ninth patient, severely potassium depleted, was treated with equal amounts of sodium and potassium from the outset. Transient intracellular migration of sodium was observed, but sustained metabolic alkalosis was not.

These observations, to be demonstrated by charted data, are in accord with the animal studies of Cook, Holiday, and others. They illustrate the effect of potassium depletion in increasing susceptibility to intracellular sodium intoxicaton and metabolic alkalosis. They make it appear desirable to keep to a minimum sodium-rich potassium-poor periods of therapy and to administer fluids containing these ions in physiologically equivalent amounts as soon as it is safe to do so.

A Comparison of Sodium and Combined Sodium Plus Potassium Therapy in Acutely Dehydrated Normal and Potassium Depleted Rats. HERMAN SPATER,* ANN HUNT,* ROBERT TODD,* NATHAN B. TALBOT, Harvard.

It has been demonstrated repeatedly that severely depleted and dehydrated patients may fail to do well until provided with appreciable amounts of potassium as well as sodium salts, in company with sugar and water. The present studies were undertaken in an effort to determine how potassium exerts this influence.

These studies were carried out on two groups of rats, of which one was normal while the other had been rendered potassium deficient by feeding a potassium-free sodium-replete diet for 25 days. Rats from each group were depleted by fasting and thirsting for three days. Such depleted rats were then given for two days, per square meter per day, 90 m-mol. of NaCl or 40 m-mol. each of NaCl and KCl. The results based on carcass analysis are summarized in the following table.

The inclusion of potassium did not alter the effects observed in the normal rats given NaCl after fasting and thirsting. Administration of Na salts alone to fasted and thirsted potassium-depleted rats led to overexpansion of extracellular volume with no change in cellular water and to persistence of cellular sodium and potassium concentration abnormalities. These animals did poorly and showed peritoneal edema. While provision of sodium plus potassium also led to overexpansion of the extracellular volume of potassium depleted, fasted and thirsted rats, it resulted in a decrease in intracellular volume and in nearly complete restoration of their cellular potassium and sodium concentrations. These rats showed a marked increase in vitality shortly after this repair therapy was started.

It is concluded that provision of potassium in addition to sodium exerts its beneficial influence on the potassium-deficient organism by restoring cellular electrolyte concentration and hence probably cell function to normal, rather than by causing extracellular or intracellular volumes to be restored to normal.

The Identification of the Conjugated Corticoids in the Serum of Children. R. KLEIN, J. FORTUNATO,* Z. LARON,* and C. PAPADATOS,* Pittsburgh.

One hundred fifty milliliter pooled aliquots of serum obtained from children after intravenous administration of ACTH have been hydrolyzed with beta-glucuronidase and acid after the free corticoids have been removed. Presumptive identification has been made of the conjugated corticoids utilizing the mobility of the compounds on paper chromatography, staining characteristics and the Zaffaroni sulfuric acid chromogen technique. Identified by these methods among the corticoids released by beta-glucuronidase hydrolysis have been 3-alpha, 17-alpha, 21-trihydroxy pregnane, 11, 20-dione (tetrahydro E), 3-alpha, 11-beta, 17-alpha, 21-tetrahydroxy pregnane, 20-dione (tetrahydro F), and 3-alpha, 21-dihydroxy pregnane, 11, 20-dione, (tetrahydro A). When acid hydrolysis was used, small amounts of tetrahydro E and F were identified by their mobility on paper and staining characteristics alone.

	Extracellular H_2O		Intracellular H_2O		
	Volume, Ml/Rat*	Na, MEq/L.	Volume, Ml/Rat*	Na, MEq/L.	K, MEq/L.
Normal Rats					
(A) Control	24	141	58	20	178
(B) Fasted and Thirsted	18	145	34	25	186
(C) Na-Cl treated	20	142	25	43	181
(D) Na-K-Cl treated	18	143	28	45	180
K+ Depleted Rats					
(A) Control	21	146	50	53	127
(B) Fasted and Thirsted	15	159	42	57	137
(C) Na-Cl treated	23	151	42	44	143
(D) Na-K-Cl treated	22	149	38	31	173

* All values per 100 gm. total, degutted animal.

The Salt-Losing Hormone of Newborn Infants. R. KLEIN, P. TAYLOR,* Z. LARON,* C. PAPADATOS,* J. FORTUNATO,* and C. BYERS,* Pittsburgh.

The unusual hormone found in the urine of newborn premature infants reported in the abstract of last year's meeting in Quebec has been separated into two corticoid materials. When these fractions were injected into intact rats along with suitable controls and standard hormones, one of them produced a sodium diuresis on the day of injection.

The staining characteristics of this hormone have been described in previous communications. However, the ultraviolet absorbing quality previously reported actually does not belong to this hormone but to another material from which it is separable on rechromatographing on the Zaffaroni toluol-propylene glycol system.

Plasma Protein Sparing Effect of Fats and Carbohydrates. DAVID GITLIN and CHARLES A. JANEWAY, Harvard.

Groups of litter-mate mice were placed on various synthetic diets. Of the diets tested, protein made up 0 to 25% of the total calories and fat and/or carbohydrate accounted for the remainder. The diets were supplemented, of course, with appropriate salts and vitamins. Mouse albumin and γ-globulin were labelled with I^{131} and given to the recipient mice intravenously. By using a Texaco-type counter having a well 2 inches in diameter, it was possible to count the radioactivity in the whole mouse without resorting to bleeding; whole body counting also eliminated some of the problems associated with intravascular-extravascular mixing and changes in the sizes of the various body plasma protein pools associated with changes in weight.

It was found that a diet sufficient in calories but without protein resulted in a decrease in plasma albumin catabolism as well as a decrease in the synthesis of albumin; the calories, of course, were supplied by fat or carbohydrate. A decrease in albumin catabolism was also noted in those mice on a diet markedly deficient in calories, but otherwise well balanced; in these instances, however, the fall in catabolism was much less than that seen in the protein-starved mice receiving adequate calories supplied by fat or carbohydrate. A situation resembling caloric starvation was noted in mice made diabetic with alloxan and in baby mice abruptly weaned from their mothers, although they were taking the chow diet. Attempts to induce plasma protein conservation with testosterone or estrone were unsuccessful. Diet had little effect on the metabolism of γ-globulin and this is in accord with findings in starvation in humans.

It would seem that the nitrogen-sparing effect of carbohydrates and fat may be due in part to a decreased catabolism of certain proteins. Contrary to our expectations, starvation with depletion of carbohydrate and fat stores resulted in a decrease in the catabolism of certain proteins rather than an increase.

Duodenal Motility in Infants and Children. GIULIO J. BARBERO,* JEAN MCGAVRAN,* and IH CHIN KIM,* Pennsylvania. (Introduced by Wallace McCrory)

A study of duodenal activity was undertaken to obtain some understanding of normal physiological activity and functional derangements in diarrhea, malnutrition, and malabsorption states.

The method of study utilized double-lumen Miller-Abbot tubes without balloons placed in the duodenum under fluoroscopic guidance. Intraluminal pressure recordings were obtained by attaching these tubes to Stratham strain gauges which were connected with a four-channel Sanborn recorder equipped with a series of strain gauge amplifiers. Body activity was simultaneously recorded by a pneumograph attached to the same system.

The subjects consisted of 50 infants and children who were free of gross intestinal disease, 10 infants with cystic fibrosis, 5 children with advanced celiac disease. Five patients before and after an acute bout of diarrhea were also studied. In addition, an opportunity to observe lower small-bowel function was offered by the study of two patients with ileostomies.

Twenty-five subjects were fed milk to determine the response in the duodenum. Cholinergic and anti-cholinergic responses produced by drug injections in two groups of 10 children were observed. The effects of sleep, activity and gastric peristalsis on the duodenum also were recorded.

These studies indicated that the duodenum has a sporadic type of resting wave activity. The most characteristic motility noted consisted of bursts of waves with a frequency of 8-12 waves per minute, and a duration of one to seven minutes. These bursts were present in both the wakeful and sleep state. Feeding produced considerable irregularity of activity at the same relative frequency. This response could be differentiated from the typical responses of the colon and stomach. A description of duodenal motility under the various conditions studied and in a number of intestinal disturbances will be presented and considered.

Oxygen Toxicity and Liver Necrosis. LEWIS A. BARNESS, DONALD PIOUS,* and PAUL GYORGY, Pennsylvania.

The importance of oxygen toxicity in pediatrics, especially in regard to prematures, is established.

The relationship of vitamin E, an antioxidant, to oxygen toxicity has been studied.

Thirty male weanling rats were placed in an atmosphere containing 60%-70% oxygen, and thirty rats were kept in room atmosphere. All rats were placed on a vitamin E-deficient, necrosis-producing diet.

Hemolysis of red blood cells with dialuric acid, a measure of vitamin E activity, was determined serially in both groups of rats. The rats in oxygen grew less well than the controls, and had a negative hemolysis test, significantly longer than the control animals. This tends to indicate that vitamin E activity persists longer in those animals subjected to high oxygen concentrations than in those at ambient oxygen concentration.

Twenty rats were studied simultaneously for blood catalase activity. No significant relationship was found between blood catalase and either oxygen administration or red cell hemolysis.

Twenty rats were studied with respect to development of liver necrosis. At the end of 40 days, all the rats in oxygen were dead, 9 of 10 having liver necrosis. At the same time, 5 of 10 controls were dead, none with liver necrosis. These data indicate that one of the effects of oxygen on young rats on a deficient diet is the acceleration of the development of liver necrosis and death.

Previous observers have described effects of oxygen on the liver including destruction of sulfhydryl enzymes, and venous congestion of the liver.

The relationship of the development of liver necrosis in young rats on vitamin E deficient diet and effects of oxygen in young babies with low vitamin E concentrations is unknown.

Dietary and Storage Factors in Nutritional Iron Deficiency Anemia. JEAN P. DAWSON,* and JANE F. DESFORGES,* Tufts. (Introduced by Louis K. Diamond)

There are reports which suggest that infants normally approach a state of marginal iron deficiency during the first two years of life. This study was undertaken to determine the relative importance of decreased iron stores at birth and poor diet in the development of overt iron deficiency anemia during this critical period.

A group of 56 infants with proved iron deficiency anemia were studied. Age, race, sex, birth weight, growth rate, duration of gestation, and dietary pattern were tabulated. In addition, serum iron and iron-binding capacities were measured in certain of the patients, their mothers, and suitable controls.

At least 33 infants had a history of poor diet and two-thirds of these were found to have a combination of excessive milk intake and decreased solids. In 8 patients the diminished solid intake was the only abnormal factor in the diet while in only two was there excessive milk intake with normal solids. In 18 cases abnormal diet was the single contributory factor.

Serum iron and iron-binding capacity were measured in 22 mothers of anemic infants. A low serum iron with normal iron-binding capacity was demonstrated in eight of these, only four of whom were anemic. In a control group of 21 mothers of nonanemic babies, 3 were found to have a low serum iron, one of them being overtly anemic. In no case was iron deficiency in the mother the single demonstrable cause of iron-deficiency anemia in the infant. Moreover, 11 of the mothers of the iron-deficient patients were known to have received iron therapy during the last trimester of pregnancy.

Thus, low iron stores at birth could be implicated as the single cause for iron-deficiency anemia in infancy in only two cases, both on the basis of low birth weight, while abnormal diet alone was implicated in 18 cases. Combined etiology for the anemia was found in 21 patients.

It would seem then that poor diet is a more frequent basis for iron deficiency anemia of infancy than inadequate iron stores at birth, but that the latter may frequently be a contributing cause of iron-deficiency anemia in the presence of an abnormal diet.

Observations on Dietary Treatment of Five Cases of Phenylketonuria. FREDERICK A. HORNER,* CHARLES W. STREAMER,* Colorado. (Introduced by John A. Lichty)

Five children with phenylketonuria have been under continual dietary treatment for 7- to 15-month periods. These patients fall into three age groups: two 5-year-old children; two 2-year-old children, and an infant sibling of one of the first group. None of these cases has been institutionalized.

Evidence of the metabolic abnormality was demonstrated by the presence of phenylketone bodies in the urine and a markedly elevated serum phenylalanine in all patients. In four of the children, severe mental impairment was confirmed by psychological evaluation. The fifth patient demonstrated no evidence of retardation at 7 weeks of age when the presence of the metabolic defect was confirmed. After three weeks on a phenylalanine-free diet, the abnormal urinary metabolites disappeared and the serum phenylalanine level reached the normal range, 2-5 mg/100 ml. At that time, phenylalanine was restored to the diet in the form of natural protein in amounts just sufficient to maintain the serum phenylalanine at normal or near normal range.

Treatment of the two oldest children has been in progress since February, 1955. These children have shown marked behavioral improvement, rapid language development, social adaptability, and sustained monthly increments in psychological quotients. The 2-year-olds were placed on therapy in

November, 1955. Observations to the present indicate rapid improvements in attention span, motor activities, and emotional responses. Motion pictures demonstrating the progress of these two children will be shown.

The fifth patient, treated since March, 1955, when 2 months of age, has followed a developmental pattern of a healthy infant. Motion pictures demonstrating his activity at varying age periods will be shown.

The responses noted in these children tend to support previously reported findings which suggest that impaired mental function in phenylketonuria is secondary to the metabolic error and not a primary amentia. The apparent healthy development of the infant treated since the age of 2 months may be most significant.

Chronic Nonspecific Diarrhea in Infants and Children Treated with Diiodo-Hydroxyquinoline. SIDNEY Q. COHLAN, New York Univ.

The data presented results from a preliminary investigation and a subsequent double-blind placebo study of the use of Diiodohydroxyquinoline (Diodoquin) in the treatment of 82 consecutive cases of chronic nonspecific diarrhea.

In the preliminary study 40 infants and children (6 months to 3 years of age) with chronic nonspecific diarrhea were treated with Diiodohydroxyquinoline. The syndrome was characterized by a history of continuous or intermittent, loose to "mushy" foul stools of two months to one year's duration. Repeated laboratory investigation failed to yield evidence of parenteral infection, parasitic infestation or intestinal infection with the usual enteric pathogens. These patients had been variously diagnosed as; mild celiac syndrome, starch intolerance or intestinal allergy. Dietary restriction (banana, high protein, low fat, starch and wheat free) with and without oral antibiotics afforded some stool control, but moderate to severe exacerbations were frequent.

A marked improvement in consistency, frequency, and odor of stools was observed in 29 of 40 patients treated with 3.2 grains of Diiodohydroxyquinoline administered three times daily. Good response occurred within one to four days of onset of therapy after which a full diet could be introduced without relapse. There were six therapeutic failures and response was equivocal in five cases.

Experimental therapeutic "trials" consisting of a period of response to Diiodohydroxyquinoline with subsequent relapse following withdrawal of medication was observed in 24 cases with three consecutive trials in one patient, two trials in 10 patients and one trial in 13 cases.

The double-blind placebo study in 41 subsequent cases of chronic nonspecific diarrhea resulted in a therapeutic correlation of 53% with 22 cases responding to drug but relapsing on placebo. There were 18 failures including 12 patients who did not respond to drug or placebo, 2 patients who responded to placebo, and 4 cases that responded to drug but did not relapse on placebo.

The results seem to indicate that Diiodohydroxyquinoline is useful as a nonspecific agent which may effect some fundamental mechanism common to nonspecific diarrheas. One possibility being explored is the relationship of the qualitative and quantitative differences in the normal intestinal flora in this syndrome and the effect of Diiodohydroxyquinoline on this bacterial pattern.

Hearing Loss Following Poliomyelitis. RANDOLPH BATSON* and FREEMAN E. MCCONNELL,* Vanderbilt. (Introduced by Amos Christie)

Disturbances of the special senses are rarely described as being associated with poliomyelitis. This has been true in spite of demonstrable central nervous system lesions that would suggest such a possibility. Our study shows that directly or indirectly severe poliomyelitis produces a hearing loss which follows a consistent pattern and is greater in the more severely disabled persons.

Thirty-seven extensively paralyzed poliomyelitis patients underwent detailed audiologic analyses in order to determine the precise status of auditory acuity. All patients had moderate to severe degrees of respiratory failure and the great majority had been disabled for several months. Twenty-five of the group were tested in a sound-isolated test chamber. Twelve were tested in a quiet room, since they could not be moved from the respiratory division of the hospital. Pure tone audiometric tests for air and bone conduction were given all patients. In order to confirm these results speech reception and discrimination tests were given the 25 patients who could be transferred to the audiology clinic.

Results of testing show a consistent pattern of mild but significant impairment of hearing for both pure tones and speech. The audiometric contour was typically characterized by a flat line from 125 c. p. s. through 2000 c. p. s. followed by a lowering of the threshold curve and then a general rise back to a normal level from 4000 c. p. s. through 8000 c. p. s. The probability of this defect being of neurogenic origin is suggested by equivalent lowering of bone conduction thresholds.

The audiometric data were subjected to statistical analysis, and the results were studied in relation to other disabilities such as extent of paralysis, loss of vital capacity, and duration of the illness. Other possible influences such as drug therapy and the use of respiratory aids have been analyzed. No conclusions can be reached as to the pathogenesis of the hearing loss; however, the data suggest a neurogenic defect possibly produced by the poliomyelitis virus or by hypoxia.

One poliomyelitis patient with mild but definite hearing loss died. Central nervous system structures that relate to hearing have been studied and photomicrographs of the tissues are available.

Neonatal Hepatitis: Studies in Human Volunteers to Evaluate the Presence of Transmissable Disease-Producing Factors. JOSEPH D. BOGGS,* JOHN A. BIGLER, CHARLES GARRIS,* and JAMES M. KIDD,* Children's Memorial Hospital.

Prolonged obstructive jaundice in infancy not associated with erythroblastosis fetalis or biliary atresia is not infrequently seen in the pediatric hospital. The clinical picture is characterized by the onset of jaundice in the first weeks of life, dark urine, acholic stools, and moderate enlargement of the spleen and liver. Histologic examination of the liver reveals focal or widespread hepatocellular degeneration, often with the formation of multinucleated liver cells or liver "giant cells." The disease state has been variously termed neonatal hepatitis, infantile hepatitis, or giant-cell hepatitis. In rare instances a similar histologic picture may be seen in older children. Reports indicate that about 60% of these infants recover; the remainder develop cirrhosis or die in the acute stages. Recently authors have suggested that this disease represents a viral hepatitis transmitted from the mother to the infant in utero. Others have suggested a congenital defect or an antigen-antibody reaction as factors in the production of the disease.

In an attempt to evaluate the possibility of a transmissible agent, such as the virus of serum hepatitis, being the etiologic factor, three families having infants with neonatal hepatitis were studied. Blood grouping studies were performed in each of the families as well as red cell fragility tests in the infants. Serum from three mothers and five affected children born of these mothers, and bacteria-free stool filtrate from two mothers and two infants were presented to groups of human volunteers. Each group consisted of five healthy white males, age 18 to 35 years.

The volunteers were examined clinically and by liver function tests weekly for six months. Findings in the human volunteers over this period are presented.

Urticarial-like Erythema Multiforme. LEO J. GEPPERT, Walter Reed Hospital.

A clinical syndrome will be illustrated which is characterized by a sudden dramatic onset in a preschool child of a giant urticarial-like panoramic erythema that does not itch and is accompanied by only minor constitutional symptoms. It is self-limited, never recurrent and no history of unusual exposure to allergens can be elicited. The syndrome was observed in 1% of all children (102 cases in a pediatric population of approximately 10,000 observed over a 10-year period). It was first thought that the disease might be more common in the vicinity of Fort Sam Houston, Texas, than the rest of the United States, since an epidemic of erythema multiforme was reported at that post in 1918. However, the syndrome was observed with the same frequency among American dependents in the Far East during the past three years.

The onset is sudden and primarily involves the trunk (especially the buttocks). The mother is usually amazed by its presence when she undresses the child, whom she had presumed to be well. The erythema then spreads to involve the face and both surfaces of the extremities. The mucous membranes are not involved. The lesions are first erythematous plaques and sheets which tend to become annular, raised, and violaceous. Edema of the hands, feet, and face appears later. Only 60% of the patients had fever. When the temperature was elevated, it was at its maximum on the second day and exceeded 102 F in only 13% of the cases. The white blood count was elevated in 50%, but over 15,000 in only 10%. Eosinophilia over 3% was rarely observed. The sedimentation rate was elevated in 40%. The duration of the disease was three to five days in 80% of the cases. No cases lasted longer than seven days. There were no recurrences. There were no important complications and no fatalities. Seventy per cent of the cases were between the ages of 1 and 5, and 25% between the ages of 3 and 4. Sixty per cent were males. Five per cent were doctors' children (whose parents, incidentally, were the most worried). The disease occurs throughout the year with peaks in April and October.

Investigations were negative for parasites, unusual bacterial flora in the nasopharynx, urine and blood cultures, chest films, EKGs, routine agglutinations, heterophiles, Wassermanns. There was no rise in antistreptolysin titre. No circulating antigen could be demonstrated in the sera of 10 cases using the Prausnitz-Kustner phenomenon at intervals of 48 hours and a week. Nasopharyngeal washings and sera were inoculated into the scarified cornea of a rabbit, into suckling mice, guinea pigs and on the choriallantoic membrane of embryonated eggs. No virus was isolated. Adrenaline and antihistominics have no effect on the progress of this rash. ACTH is effective but use is not warranted, since the disease is self-limited, with a predictable prognosis. No local therapy is effective and none is required, since itching is minimal in spite of the urticarial appearance of the lesions.

These observations more sharply delineate the natural history of this syndrome, but further investigation is necessary to establish its etiology.

Acid Soluble Nucleotides in Normal and Leukemic Blood. HARRY A. WAISMAN, Wisconsin.

Column chromatography methods were used for the separation of acid soluble nucleotides in both normal and leukemic blood. Proteins were precipitated with perchloric acid and the supernatant material placed on a Dowex-1 formate column, and the nucleotides were eluded with formic acid and ammonium formate. Profiles were obtained which were the result of reading each 5 cc. eluate fraction at 260 mu in a Beckman DU spectrophotometer where a "peak" in the profile appeared. Readings at 275 mu were also taken. The ratio of absorption at 275 mu to the absorption at 260 was used as an aid to identify the nucleotides. Each "peak" of absorption represented a single nucleotide or a mixture of nucleotides. The results show that increased amount of what was apparently an ATP (or mixture of ATP and another nucleotide) were found in many of the leukemic bloods. Lysis of normal blood caused little change in the profile. Lysis of leukemic blood caused some lowering of pyrophosphate "peaks" resulting in increase of "peaks" with lower phosphate contents. Individual fractions of red blood cells, white blood cells, and plasma were also examined for nucleotide content. White blood cell fractions provided several "peaks" which are now in the process of identification. Typical profiles will be presented.

Plasma Fibrinogen Levels in the Normal Newborn Infant. PAUL M. TAYLOR,* Pittsburgh. (Introduced by Stuart S. Stevenson)

It is the purpose of this paper to present data on the plasma fibrinogen concentrations of a group of normal newborn infants. A survey of the literature shows that this subject has been studied inadequately, especially with regard to factors that might affect the infant's fibrinogen level. Some of these factors are considered in this report.

Plasma fibrinogen concentrations have been determined by the clot density method on a series of 45 normal infants for the first several days of life, and on 36 of their mothers during the first 12 hours postpartum. The mean value for the infants on the first day was 231 milligrams per cent, as compared with 440 milligrams per cent for the mothers, and 280 milligrams per cent for a control group of 30 healthy adults. In no instance did an infant's level equal or exceed his mother's. There is no correlation between the height of the maternal and infant values.

A slight increase in the mean fibrinogen level of the infants is seen in the first 3 days of life. Daily fluctuations may be marked in the individual infant. Sex, color, and birth weight do not influence the infant's initial fibrinogen value.

A correlation may exist between the initial fibrinogen concentration of the infant and the degree of hepatic immaturity. Nineteen infants were observed carefully for the appearance of jaundice. The mean level of 4 infants who developed jaundice was 217 milligrams per cent, as compared with 232 milligrams per cent for the 15 nonicteric infants. This is being studied further at present.

Dam and others reported greater prolongation of prothrombin time in infants who showed signs of fetal distress than in those who did not. Although no infant in our series manifested intrauterine distress, we studied three who had delayed onset of respirations. Depressions of fibrinogen values did not occur in these infants.

The Alpha-2- and Gamma-Globulins in Childhood Tuberculosis. CHARLOTTE B. MARKER,* New York University. (Introduced by M. H. D. Smith)

In a study now in progress, the data thus far obtained on over 50 children with various forms of childhood tuberculosis indicate that the alpha-2- and gamma-globulins are initially elevated in proportion to the severity of the disease, with two exceptions: (1) In patients with meningitis, gamma-globulin levels were initially depressed in all cases. (2) In miliary tuberculosis, the more severely ill patients had similar findings. In the less severely affected cases, alpha-2 and gamma were initially elevated.

As the patients improved, the levels of both alpha-2 and gamma decreased. In meningitis, however, as the patients improved the gamma-globulin rose to levels approximately twice the normal mean. With continued improvement, the level gradually dropped. The alpha-2, in meningitis as in the other forms of childhood tuberculosis, decreased with improvement of the patient. Thymol turbidity curves paralleled those of the gamma-globulins. The erythrocyte sedimentation rate did not show any consistent correlation with activity. The chemical methods used for the determination of these globulins correlate well with electrophoretic studies. There is suggestive evidence that, when the gamma-globulin is initially elevated, it tends to drop more quickly in cases receiving isoniazid than in those not treated.

These serum protein changes, while nonspecific, show promise of being the best laboratory tests presently available to indicate activity and prognosis in childhood tuberculosis.

Studies on Monosaccharides Utilizing Chromatographic Methods. STANLEY W. WRIGHT,* ROBERT A. ULSTROM,* and JOSEPH SZEWCZAK,* University of California. (Introduced by Nathan J. Smith)

Chromatographic techniques have been developed which allow the qualitative demonstration of monosaccharides as they occur in the blood and other body fluids. These methods are applicable to study

of the utilization of monosaccharides in the infant. Excellent results have been obtained in identification of blood glucose, and, following their oral or intravenous administration, fructose and galactose. The relatively rapid disappearance of the fructose from the blood suggests its rapid utilization. Galactose has been demonstrated in the blood of normal infants following administration of galactose, as well as in the galactosemic infant.

A reducing substance migrating at the same rate as fructose has been found in infant cord bloods; further identification is now in progress. Studies on breast milk have shown large quantities of lactose, as would be expected, plus small amounts of glucose.

The Urine Volume and Solute Concentration in Children with Pitressin-Resistant Diabetes Insipidus Given a Low Mineral Solute Milk. H. G. KEITEL* and J. BLAKELY,* National Institute of Health.

Two males, aged 1½ and 2½, and one female, aged 9, were studied. All had a history of polyuria since birth, continued to excrete hypotonic urine following Pitressin and were undersized for age and under weight for size. Urging an increase intake of regular food was unsuccessful.

The diet was changed over a 2-3 week period by gradually increasing the fat and sugar content of milk, which constituted a large part of their usual intake. Water and food were allowed ad libitum. The caloric intake increased up to 40% and the oldest patient eventually became mildly obese.

A 55%-75% reduction in the rate of urinary excretion of solutes followed the use of the high caloric, low solute milk. However, only a 12%-16% reduction in urine volume was noted since the solute concentration of urine fell progressively from 88-106 mOsml. to 21-55 mOsml., and the free water clearance (C_{H_2O}) did not change appreciably.

Anaemia in a Newborn Infant Due to Placental Hemorrhage in Utero. H. H. GUNSON,* Toronto. (Introduced by A. J. Rhodes)

Wiener suggested in 1948 that occult placental hemorrhage in utero could cause anemia in a newborn. It was not until Chown demonstrated the presence of fetal cells in the maternal circulation that proof for this concept was obtained.

A member of the pediatric staff of this hospital, Dr. B. Laski, has collected over 20 cases of anemia in the newborn period unassociated with hemolytic disease, in which a presumptive diagnosis of hemorrhage from the fetal side of the placenta has been been made. In 1955, the mother of a newborn infant suffering from unexplained anemia from the time of birth was investigated, and the presence of fetal cells in her circulation was shown by differential agglutination tests.

The mother was Group A Rh negative and the child was Group O Rh positive. By means of Ashby counts, at regular intervals during the postpartum period, the life of the fetal red cells in the mother's blood was followed. Their presence could be detected for over 70 days. At the end of this time the mother developed Rh antibodies, which were not previously present, of a type similar to the Rh antigens possessed by the child.

This case illustrates that anemia in a newborn infant may be caused by transplacental hemorrhage in utero and from clinical experience these cases appear to occur more frequently than has been thought in the past. In only a small number of cases, however, can the diagnosis be confirmed by differential agglutination tests. The development of Rh antibodies by the mother subsequent to this transfusion of fetal cells strengthens the theory that this may be the mechanism of Rh antibody formation as a result of pregnancy. In the majority of cases in which the mother develops Rh antibodies, however, the quantity of fetal blood entering the maternal circulation is probably small and will cause no significant anemia in the child.

The Induction of in Vitro and in Vivo Calcification in Bones of Children Suffering from Vitamin D-Resistant Rickets Without Recourse to Large Doses of Vitamin D. D. FRASER,* N. T. JACO,* E. R. YENDT,* J. D. MUNN,* and EDITH LIU,* Toronto. (Introduced by A. J. Rhodes)

We have recently been confronted with certain problems in the therapy of vitamin D-resistant rickets, and the experiments to be reported were the outcome of our investigation of some of the physiological mechanisms concerned with the calcification of rachitic bone in this disease.

Our initial experiments, carried out in vitro, were designed to determine the role of serum calcium and inorganic phosphorus in the deposition of bone salts. A rachitic costochondral junction was removed from each of three young children suffering from untreated vitamin D-resistant rickets. Using the techniques of Shipley, Kramer and Howland, as modified by Yendt, Connor and Howard, slices of the junction were incubated in various natural and synthetic media at 37.5 C for periods ranging from 26 to 48 hours, after which the rachitic epiphyseal cartilage was examined for the presence of calcification. Although incubation of the slices in the sera of the rachitic patients produced no changes, a readily demonstrable deposition of bone salts occurred at the provisional zone of calcification when incubation of an adjacent slice was carried out in the serum of normal children. Similar calcification occurred in slices which were incubated in the sera of the patients provided that the concentrations of calcium and phosphorus were artificially adjusted to the normal range.

This in vitro demonstration, not previously reported in the human, suggested the possibility that adjustment of the patient's circulating calcium and phosphorus concentrations to normal might produce improvement in the mineralization of his skeleton without recourse to the administration of the usual large doses of vitamin D. Two untreated vitamin D-resistant children, both with normal total serum calcium and with typically low serum inorganic phosphorus concentrations, were given a continuous intravenous infusion of isotonic sodium phosphate pH 7.3-7.4, the formulation of which was kindly suggested by Dr. J. E. Howard. The rate was adjusted to maintain the serum inorganic phosphorus level above 5.0 mg/100 ml. for periods of five days and seven days, respectively. In both cases the establishment of a normal serum phosphorus concentration was followed almost immediately by a fall in total serum calcium concentration. Within five days radiological evidence of healing was readily demonstrable in the metaphyses, and the serum alkaline phosphatase level gradually fell to within the normal range.

After cessation of intravenous therapy, biochemical evidence of active rickets rapidly returned. On the other hand, the improved radiological picture was maintained for two months, after which slight "fraying" of the metaphyses again became gradually evident at the knees and wrists. Because of the gratifying results of phosphate therapy we are planning to assess the value of combining this with the use of vitamin D, and are searching for improvements in the methods of phosphate administration.

Although the practical value of these findings is not yet established, we believe that they are of some theoretical interest. Since the patients under study were not receiving vitamin D supplements, it is evident that in vitro and in vivo calcification can be induced in vitamin D-resistant rickets by establishing physiological levels of serum calcium and phosphorus and that an excessive concentration of vitamin D in bone matrix is not obligatory for healing.

Saliva Chloride in the First Year of Life. RAYMOND L. CLEMMENS,* IRENE IVINS,* and SAMUEL P. BESSMAN, Maryland.

Utilizing a simple test of parotid saliva chloride concentration, several hundred tests have been made on children in the first year of life. The average chloride levels found diminish with age, reaching a stable adult mean at around one year. Although most infants have adult levels at the end of the first month, prematures have a persistently elevated level. Increased salivary chloride has been found in patients with cystic fibrosis of the pancreas and the highest levels obtained on infants have been measured in patients with meconium ileus. Patients with adrenal insufficiency have increased values.

A number of precautions must be taken to insure proper assay of saliva chloride. Regurgitation will cause marked contamination, as will testing immediately following feeding. The child's mouth must be rinsed with distilled water, by letting him take a half ounce by mouth. Five minutes after this water feeding, the saliva is collected. When these precautions are observed, and when chloride free cotton is used, consistent values can be obtained.

A Comparative Study of the Metabolism of Glucose and Fructose in Infants. ROBERT KAYE, MARGARET L. WILLIAMS,* and GIULIO BARBERO,* Pennsylvania.

A series of reports, based on work in adults, have indicated that fructose offers advantages over glucose as the preferred carbohydrate for parenteral administration.

In view of the known ability of infants to utilize considerably greater quantities of glucose per unit of body weight than adults, it seemed worth while to determine whether or not evidences of superior utilization of fructose could be demonstrated in this age group.

The data reported here are derived from a series of 33 infusions administered to 21 infants, most of whom were under 9 months of age. The infusions were administered intravenously at a relatively constant rate by means of a pump for periods of six hours, with the exception of four infusions of four hours duration. All infused solutions contained equal concentrations of a hypotonic electrolyte mixture containing Na, K, Cl, and PO_4. The carbohydrate concentration of the solutions was varied in order to provide different levels of carbohydrate intake at constant rates of infusion. Urine was collected quantitatively, and appropriate analyses were carried out on the blood and urine.

Fructose was as well utilized as glucose when administered at rates (1.0gm/kg/hr.) within the known capacity of the infant for essentially complete utilization of glucose; 1.6% and 3.6%, respectively, of the glucose and fructose infused was excreted in the urine. A significant difference in utilization in favor of fructose was noted in 16 infusions given at an average rate of 2.0gm/kg/hr. to eight infants who received both fructose and glucose infusions; 20% and 10% of the carbohydrate infused was excreted in the glucose and fructose experiments, respectively ($P=<0.02$).

Disadvantageous aspects connected with the demonstrated superior utilization of fructose were noted. The subjects receiving fructose excreted 126% of the Na infused, in contrast to 79% for those receiving glucose ($P=<0.01$). In addition, significant changes in pulse and respiratory rate and liver size were noted with fructose, but not with glucose infusion. Furthermore, evidence of profound metabolic acidosis occurring during fruc-

tose infusion was demonstrated by the finding of a blood pH of 6.9 and CO_2 content of 8mEq/l.

As it appeared most likely that these findings were the result of a greater accumulation of the carbohydrate metabolic intermediates, lactic and pyruvic acids, this possibility was investigated in 10 subjects. Determinations were carried out of Na, K, Cl, glucose and/or fructose, pH, CO_2 content, lactic and pyruvic acids at intervals in blood and of the above with the exception of pH and CO_2 content in the total urinary output. In the fructose infusions, pH fell from an initial value of 7.35 to 7.23, CO_2 content declined 6mEq/l, and lactic acid rose 36mg.% (4mEq/l). During the infusion of glucose there was no change in pH or CO_2 content, and a rise of 18mg.% (2mEq/l) in lactic acid. Pyruvic acid changes were similar but of smaller magnitude. The subjects receiving fructose excreted in the urine an average of 44mg/kg. of lactic acid compared to 4mg/kg. for the subjects infused with glucose.

The results here reported suggest that there are certain disadvantageous metabolic effects encountered in administering carbohydrate infusions at rates beyond the tolerance of infants to glucose and that these undesirable effects are more marked with fructose than glucose.

Case Reports

Cholelithiasis Complicating Sickle-Cell Anemia

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MUCH has been written concerning the occurrence of cholelithiasis in patients with congenital hemolytic anemia, but cholelithiasis complicating sickle-cell anemia is rarely encountered.

Weems,[1] in 1945, pointed out that gallstones were occasionally found at autopsy in patients with sickle-cell disease, and he described two adults and a 13-year-old boy in whom gallstones had definitely been demonstrated by x-ray. Although no statement was made, it seems fairly safe to assume that these patients had been treated with multiple transfusions, as it is only recently that the trend away from this type of therapy has occurred. In a review of autopsy findings from 44 cases in the literature Weems found 12 instances of cholelithiasis, only one of which was in the age group from 11 to 20 years. He advanced the theory that cholelithiasis was responsible for some of the acute and chronic abdominal symptoms in these cases.

Tomlinson[2] also in 1945 reported the autopsy findings in 11 patients with sickle-cell anemia who ranged in age from 7 months to 18 years at the time of death. Gallstones were found in only the oldest patient. Henderson[3] in a review of 54 cases found signs and symptoms of cholelithiasis to be the presenting complaint only once in the group. Wintrobe[4] in his textbook of hematology gives only brief mention of gallstones as a possible complication of sickle-cell disease. In 1955, Mintz[5] and associates reported two cases of cholelithiasis discovered by means of routine cystograms performed on a series of 20 children known to have sickle-cell disease. Their first case was a 14-year-old Negro boy who had received "transfusions on numerous occasions" and had the onset of attacks of abdominal pain at the age of 8 years. The second case was a 10-year-old boy who had received only one blood transfusion and had only one episode of abdominal pain at the age of 5 years.

The following additional case is reported in order to demonstrate the complication of cholelithiasis occurring in a relatively young patient suffering from sickle-cell disease.

Report of Case

A 13-year-old Negro girl was first seen at Harbor General Hospital on Oct. 18, 1954 because of back and abdominal pain of 16 hour's duration. The pain was of a recurrent cramping nature located primarily in the epigastrium and across the lumbar area of the back. There was no vomiting, diarrhea, or constipation associated with the pain.

Past history revealed that the diagnosis of sickle-cell disease had first been made in 1941 at the age of 5 months in another hospital, and during the next 6 years, until 1947, she was followed in that hospital. She had been admitted numerous times in sickle-cell crises, and her record from the hospital showed that she had been transfused a total of 50 times during that six-year period. From 1947 until the time she was first seen by us in 1954 she was followed in a second hospital, during which time she again received transfusions approximately every two to three months because of sickle-cell crises.

Family history revealed the mother was known to have the sickle-cell trait. Information on the patient's father was unobtainable.

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Physical examination on admission revealed a slender but well-developed Negro girl in moderate distress with abdominal and back pain. Temperature was 99 F, pulse rate 90 per minute, respirations 25 per minute, BP 100/40. The sclerae were slightly icteric. The chest was clear. The heart was not enlarged to percussion, but a Grade 2 blowing systolic murmur was heard at the apex. The liver edge was palpated 6 cm. below the right costal margin in the midclavicular line. The spleen was not felt. The skin of the lower extremities revealed numerous small scarred areas which were believed to have previously been ulcers. The neurological examination was normal.

Laboratory studies were as follows: WBC 12,800 per cu. mm. with a differential count of 1 band, 73 polymorphonuclears, 15 lymphocytes, 3 monocytes, 7 eosinophiles and 1 basophile. Red blood cells 3,250,000 per cu. mm. Hemoglobin 8.3 grams per 100 cc. Hematocrit 21%. Reticulocytes 22.6%. Marked sickle-shaped erythrocytes were present on the stained blood smear. Cephalin flocculation 2+ in 24 hours, 3+ in 48 hours. Thymol turbidity 2.8 units. Serum bilirubin 4.0 mg. per 100 cc. The specific gravity of the urine was 1.010; there was no bilirubin present, but urobilinogen was present in a 1:200 dilution.

Hospital Course.—The patient was given no transfusions during her hospital stay, but oral fluids were urged to 3000 cc. or more per day. She became febrile shortly after admission, the temperature reaching 102.6 F orally, but she became afebrile by the third hospital day, and at that time the complaints of abdominal pain ceased. After this she continued to do well and was discharged on the 10th hospital day to continue care in the outpatient department.

She was next seen 8 days later with complaints of generalized headache and fever of 12 hours duration. Prior to the onset of the headache she had been well and attending school. On examination the child appeared acutely ill. Temperature 104 F, pulse rate 124 per minute, respirations 24 per minute, BP 120/70. The sclerae were slightly icteric. There were diminished breath sounds over both bases. Neurological examination revealed moderate nuchal rigidity, but no other neurological signs.

A lumbar puncture was done which revealed clear fluid under normal pressure. The fluid contained 5 cells, 26 mg. per 100 cc. protein and 75 mg. per 100 cc. sugar. No organisms were seen on direct smear, and none was cultured.

Laboratory studies were as follows: WBC 29,300/cu. mm. with a differential of 73 polymorphonuclears and 27% lymphocytes. Hemoglobin 8.8 gm. per 100 cc. Hematocrit 20%. RBC 2,200,000/cu mm. Reticulocytes 20.7%. Serum bilirubin 4.0 mg. per 100 cc. Icterus index 28. Sickle-shaped erythrocytes were again noted on the direct blood smear. The urine specific gravity was 1.008, and the routine urinalysis was normal.

On this admission blood was obtained from the patient, her siblings, and mother for hemoglobin electrophoresis. Results showed the patient to have an S-S pattern, the mother S-A, a half-sister S-A, and two brothers both with S-A, (the letter S indicating a gene for hemoglobin S, and A for adult hemoglobin).

Hospital Course.—The patient was again treated with a regimen of forced fluids and antibiotics. Her headache and nuchal rigidity had disappeared by the following morning and she was afebrile and asymptomatic by the third hospital day. After this she complained at least once daily and sometimes more frequently of right upper quadrant and flank pain. There was no pattern of radiation and no associated gastrointestinal symptoms. The pain was primarily postprandial, but there was no apparent relationship to fatty foods. Because of the pain a cholecystogram was done which revealed a normally functioning gall bladder and several radiolucent areas interpreted as gallstones—demonstrated in the Figure.

Further questioning of the child and her mother revealed that apparently as early as age 7 she had had occasional episodes of paroxysmal right upper quadrant and lumbar pain in the past not associated with a sickle-cell crisis.

Because of her persistent abdominal distress it was felt that cholecystectomy was indicated. Simple removal of the stones was decided against because of the real possibility of reformation in the face of continuing active sickle-cell disease.[6] A cholecystectomy was subsequently performed, care being taken before, during, and after surgery to keep the patient well hydrated with intravenous fluids. Her postoperative course was complicated by a mild thrombophlebitis and a wound abscess which responded readily to antibiotic therapy.

The pathologist's report of the surgical specimen was as follows: "The specimen consists of a gall bladder measuring 6 cm. in length and approximately 5 cm. in circumference. The serosal surface is dull, reddish gray in color. Within the gall bladder are approximately nine black gritty stones the largest of which is 7 mm. in diameter. The mucosa is injected and in many areas it is smoothed out while in others it is velvety in appearance. The epithelium and mucosa are fairly well intact. There is a mild lymphocytic infiltration in the lamina propria.

Diagnosis.—Cholelithiasis, cholecystitis, chronic "mild."

The patient was discharged on the 15th hospital day at which time she was feeling well. She was again instructed to consume at least 2000 cc. of

Cholecystogram

fluid per day. She is now approximately 18 months postoperative, asymptomatic, gaining weight, and attending school regularly. She has had no gastrointestinal complaints since discharge.

Comment

The formation of gallstones in sickle-cell disease is probably related, as it is in congenital hemolytic anemia, to the increased destruction of erythrocytes. Hyperbilirubinemia is produced and results in excessive bilirubin excretion. Precipitation of the bile pigments in the gall bladder forms a nidus of stone formation on which more pigment is then deposited.

The aim in therapy of sickle-cell crisis is to reverse the hemolytic process as rapidly as possible which will in turn decrease the chances of complications. If this can be done without the use of blood transfusions it seems desirable to withhold transfusions, since these children are able to adapt well to relatively low hemoglobin levels and since a return to pretransfusion levels occurs within a few weeks even when blood is given. It is probable that fewer transfusions would lessen the likelihood of gallstone formation as well as other complications, such as hemachromatosis.

Sharpsteen[7] has shown that the intracellular protein osmotic pressure of erythrocytes is decreased in patients with sickle-cell crisis and that the hemolysis of these cells is reversible when the osmotic pressure of the plasma equals that of the cells. As postulated by Diamond, Smith, and Vaughn[8] and as suggested by the clinical course of our case, the crises of sickle-cell disease may be reversed by the liberal use of electrolyte-free fluids which lower the osmotic pressure of the plasma.

Summary

A case is presented demonstrating cholelithiasis as a complication of sickle-cell disease in a 13-year-old girl. Although abdominal pain is a common complaint during the course of many childhood illnesses and is especially common in children with sickle-cell disease, it is suggested that cholelithiasis be considered as a possible cause and that cholecystograms be done with this in mind. The case presented above lends support to the recent trend away from the use of blood transfusions in the management of sickle-cell crisis.

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The Metabolic Response to Burns. Eric Reiss, Elinor Pearson, and Curtis P. Artz.—p. 62.

*The Anemia of Infection: XX. The Kinetics of Iron Metabolism in the Anemia Associated with Chronic Infection. J. A. Bush, Helen Ashenbrucker, G. E. Cartwright, and M. M. Wintrobe.—p. 89.

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Virilizing Adrenal Hyperplasia: A Genetic and Hormonal Study. Barton Childs, Melvin M. Grumbach, and Judson J. Van Wyk.—p. 213.

Certain Aspects of Tyrosine Metabolism in the Young. I. The Development of the Tyrosine Oxidizing System in Human Liver. Norman Kretchmer, S. Z. Levine, Helen McNamara, and Henry L. Barnett.—p. 236.

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The Hemodynamics of Thyrotoxicosis in Man with Special Reference to Coronary Blood Flow and Myocardial Oxygen Metabolism. George G. Rowe, John H. Huston, Arvin B. Weinstein, Herman Tuchman, John F. Brown, and Charles W. Crumpton.—p. 272.

Studies on Myocardial Metabolism. V. The Effects of Lanatoside C on the Metabolism of the Human Heart. J. M. Blain, E. E. Eddleman, A. Siegel, and R. J. Bing.—p. 314.

*The Fat, Protein and Nucleic Acid Content of the Liver in Malnourished Human Infants. J. C. Waterlow and T. Weisz.—p. 346.

35:355-452 (April) 1956

The Induction of Gross Myocardial Lesions by a Coxsackie (Pleurodynia) Virus and Cortisone. Edwin D. Kilbourne, Charles B. Wilson, and Dorothy Perrier.—p. 362.

Familial Hypoglycemia Precipitated by Amino Acids. W. A. Cochrane, W. W. Payne, M. J. Simpkiss, and L. I. Woolf.—p. 411.

The Effect of Estrogen on Water and Electrolyte Metabolism. I. The Normal.—p. 423; II. Hepatic Disease.—p. 430; III. Cardiac and Renal Disease. John R. K. Preedy and Elsie H. Aitken.—p. 443.

The Anemia of Infection. XX. The Kinetics of Iron Metabolism in the Anemia Associated with Chronic Infection.—Plasma and red-cell iron turnover studies were determined in 6 patients with anemia of infection and in 10 normal patients, in an attempt to elucidate the pathogenesis of the hemoglobin loss.

These alterations have been attributed to a decreased rate of red-cell production due to a defect in the conversion of protoporphyrin to hemoglobin. There is no laboratory evidence of increased blood destruction. Varying techniques used in studying erythrocyte survival have shown conflicting results: either normal or decreased survival times. However, studies with rheumatic fever and rheumatoid arthritis, the anemia of which is similar to that of chronic infection, suggest a decreased erythrocyte life span due possibly to an extracorpuscular hemolytic mechanism.

Using the methods of Huff and co-workers (J. Clin. Invest. 30:1512, 1951), the authors determined the turnover rate of iron through the plasma and red cells, and the life span of the erythrocytes. In these patients with chronic sepsis, there was a mild degree of anemia which was neither increasing or decreasing in severity.

The patients incorporated an average of 95% of the injected radio-iron into the erythrocytes. This occurred more rapidly than in normal subjects. The rapid uptake apparently was due to the fact that the total amounts injected were considerably smaller than in previous studies, and thus did not appreciably increase the total body plasma-iron pool. However, the ultimate percentage incorporated into the red cells was the same in both groups. Body surface counting patterns of uptake and delivery by the liver, spleen, and marrow did not differ from the normals. Little radio-iron entered the liver or spleen.

The data indicate (1) that patients with infection made and destroyed each day the same amount of hemoglobin as normals. Since these patients nevertheless had a reduc-

tion of total red-cell iron, the proportion of red-cell life was shortened to some degree. (2) The modest shortening of red-cell life is not compensated for by the marrow. (A 50% increase in activity would be ample to cover the deficit and in the normal person a six to eight times increase in marrow activity is possible.) The conclusion is therefore drawn that on this basis there is a marked inhibition of erythropoiesis. This defect appears to be of greater importance in the production of the anemia than the decrease in red-cell longevity.

The Fat, Protein and Nucleic Acid Content of the Liver in Malnourished Human Infants.—Liver biopsies from 12 malnourished Jamaican babies were analyzed in an attempt to determine the composition of the fatty liver and its relationship to the severity of the clinical illness. Deoxyribonucleic acid content (DNA) was used as a fixed standard of reference for measuring protein content, since the liver appears to be constant under a wide variety of dietary conditions. The infants, malnourished on a diet of carbohydrate after weaning, rapidly developed fatty livers, and were grossly underweight. Since there was considerable subcutaneous fat remaining, the reduction in body mass consisted of muscle loss in large proportion.

Earlier work had suggested that the degree of fatty infiltration determined the severity of the disease and the prognosis. More recent results disputed this correlation. Microscopically, the cell consists of a thin rim of cytoplasm surrounding a large fat globule. Since there is always a low protein intake in these children, there may be an actual loss of cytoplasm and not merely distention of the cell by fat. Hence the hypothesis is made that there is not only a deficiency of lipotropic factors, but also a simultaneous accumulation of fat, plus a depletion of protein and other cytoplasmic elements.

Measurements to confirm this hypothesis suggest (1) a real increase in water content of the fatty liver, (2) a relatively high glycogen content, (30% of the fat-free dry weight), which is comparable to that of the cases after treatment and recovery. This confirmed the histological observation that large amounts of glycogen may be present in a cell distended with fat. This is very different from the findings in a locally prevalent "toxic" disease with vomiting and malnutrition where the liver glycogen is largely depleted. (3) On admission the infants had lost 40% of the liver protein (protein consisting of only 50% of the dried weight), on the assumption that DNA remains constant. (4) In six fatal cases including one having a biopsy 30 minutes prior to death, there was no correlation with the degree of protein deficiency. The average level in these was actually higher. The authors feel that this method of analysis gives useful statistical information in a group of cases but is not precise enough to indicate the degree of protein depletion in a single case at a given moment.

Journal of Pediatrics

48:409-544 (April) 1956

Metabolic Significance of Nervous Symptoms Due to Attacks of Vomiting with Ketosis in Children. R. Debre, P. Royer, and H. Lestradet.—p. 409.
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Investigation of a Staphylococcal Epidemic in Babies in a Maternity Hospital, and Similar Outbreaks in Other Hospitals. J. E. McCartney and T. O. R. Yates.—p. 50.
Control of an Epidemic of Acute Infective Enteritis of the Newborn. F. M. C. Forster and J. C. Laver.—p. 57.

1:77-120 (Jan. 21) 1956

*Passive Protection Against Rubella. Hugh Ward and Grace Parker.—p. 81.

Passive Protection Against Rubella.—The association of rubella in the mother in the first trimester of pregnancy with congenital defects in the fetus is well established. Attempts to protect the fetus by passive immunization of the mother have led to inconclusive results. The present study consisted of a group of 541 women exposed to rubella, and a smaller control group of 152 persons. The material used for immunization in each case was 30 ml. of serum, which was injected intravenously. The serum was obtained from adults who were three weeks convalescent from rubella. The attack rate in the passively immunized group of women was 0.9%. The attack rate in the nonimmunized

control group was 11.2%. The authors review the literature concerning previous studies on passive immunization against rubella and point out shortcomings in their own work. They conclude, however, that convalescent serum is of real value as a means of protecting pregnant women after exposure to rubella.

Metabolism, New York. Vol. 5, No. 1, Jan. 1956

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Paradoxical Hyponatremia Associated with Congestive Heart Failure and with Cirrhosis of the Liver. P. J. Talso, N. Spafford, G. Ferenzi, and H. O. Jackson.—p. 58.
*The Total Body Hemoglobin in Children and Its Relation to Calorie and Iron Requirements. W. W. Hawkins, V. G. Leonard, and E. Speck.—p. 70.
The Metabolic Activity of Adipose Tissue.—A Review. B. Shapiro and E. Wertheimer.—p. 79.

The Total Body Hemoglobin in Children and Its Relation to Calorie and Iron Requirements.—The blood hemoglobin level was measured in 1800 children 6-17 years of age inclusive. Calculation of the total body hemoglobin (the blood volume being deduced from the height and weight) showed that growth is the most important factor determining the amount of iron required by children except in girls after 13 years of age when catamenic loss is the major consideration. After puberty, boys require more iron to support the increase in total hemoglobin than do girls because the greater increase in total hemoglobin in boys outweighs catamenic loss in girls. Special consideration should thus be given to boys from 12 years of age onward to ensure adequate iron supplies.

New England Journal of Medicine, Boston

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Studies of Bacterial Throat Flora During Chemoprophylaxis of Rheumatic Fever. J. M. Miller and B. F. Massell.—p. 149.
*Current Status of the Clinical Use of Antibiotic-Vitamin Combinations. G. A. Goldsmith.—p. 165.

Application of the Antistreptolysin-O Titer in the Evaluation of Joint Pain and in the Diagnosis of Rheumatic Fever.—Although it is possible that differences of the antistreptolysin-O titers may have been due to other factors, the authors show an excellent correlation of high titers with acute rheumatic fever in this study of 648 consecutive patients admitted to the House of the Good Samaritan in Boston. Data are presented showing that 50% of the children under 17 years with rheumatic fever (Chorea Cases excluded) had significant arthritis and that 50% of the patients with arthritis had cardiac involvement.

Comparisons are made of patients with carditis, patients with rheumatic arthritis, patients with rheumatoid arthritis, and a miscellaneous group of children admitted with a major complaint of joint pain but subsequently shown to be nonrheumatic. The antistreptolysin-O titers of the first two groups were essentially similar and show of 435 children only 3 had titers of less than 50 units. In general the curve shows a sharp change at 159 units. Only 1.8% of the rheumatic children had levels below this break point. Therefore a low level is very valuable in excluding rheumatic fever.

Levels above 400 units were found in 85% of the rheumatic patients, 28% of the children with rheumatoid arthritis and 8% of the miscellaneous group (approximately the same per cent as is found in the normal child population in Boston). The use of high antistreptolysin-O titers to make a diagnosis is not, therefore, completely reliable. However, the most confusing situation arises in distinguishing rheumatic fever from rheumatoid arthritis. In this differentiation the age of onset has been very valuable since rheumatic

fever has been very rare under 4 years of age (less than 1% in this series), whereas 37% of the children with rheumatoid arthritis were under 4 years of age. The finding of a high antistreptolysin-O titer in a child from 4 to 16 years of age is very suggestive of rheumatic fever. The antistreptolysin-O titer was of no value in the prediction of heart damage.

Current Status of the Clinical Use of Antibiotic-Vitamin Combinations.—Although the combination of vitamins with antibiotics is being used extensively, this practice rests on a very inadequate basis of fact. The relationship between nutrition and infection demands more investigation since so little clear-cut information is available at this time. The problem here revolves around the following hypothesis: Does an increased vitamin intake aid most resistance to infection or improve the efficacy of the antibiotics, does infection or antibiotic administration itself alter the utilization or requirement for vitamins, or may the reverse of these take place. Most of the studies on this problem have been done in laboratory animals and must be interpreted with caution. At present it appears that a deficiency of certain vitamins is associated with an increased resistance to viral infections. Although most of the studies on bacterial infections would indicate that vitamin deficiency is associated with a lowered resistance, this was not found universally.

This review of the available literature points up the confusing and contradictory status of this problem at the present time. More information is needed on the actual effect in man of giving extra vitamins during antibiotic treatment. In the few controlled studies reported, no significant difference can be demonstrated.

Directory of Pediatric Societies*

INTERNATIONAL

Ninth International Congress of Paediatrics

President: Dr. Allan Ross, 1615 Cedar Avenue, Montreal, Canada.
Place: Montreal. Time: 1959.

International Union for Child Welfare

Chairman of Executive Committee: Judge M. Ch. de Jong, 10 Hogeweg, Wassenaar, (Holland).
Secretary General: Dr. Georges Thelin, 1 Rue de Varembe, Geneva, Switzerland.

FOREIGN

Academy of Medicine, Toronto, Section of Paediatrics

Chairman: Dr. J. D. Bailey, 140 Brown's Line, Toronto.
Secretary: Dr. John A. MacLean, 51 Eglinton Avenue East, Toronto.
Place: Academy of Medicine. Meetings: Once a month.

Asociacion de Pediatrias Espanoles

President: Dr. Rafael Ramos Fernández.
Vice-Presidents: Dr. Juan Bosch Marín and Dr. Ciriaco Laguna.
Secretary-General: Dr. Luis Navas Migueloa.
Treasurer: Dr. Angel Ballabriga.

Australian Paediatric Association

President: Dr. P. A. Earnshaw, Ballow Chambers, Wickham Terrace, Brisbane. B17.
Honorary Secretary-Treasurer: Dr. D. C. Jackson, 217 Wickham Terrace, Brisbane. B17.
Place: Canberra. Time: Yearly in April.

British Paediatric Association

President: Prof. F. M. B. Allen.
Secretary: Dr. P. R. Evans, Hospital for Sick Children, Great Ormond St., London, W. C. 1.
Place: Windermere. Time: May 8-11, 1957.

Canadian Paediatric Society

President: Dr. J. Harry Ebbs, 555 University Avenue, Toronto.
Secretary-Treasurer: Dr. J. C. Rathbun, 526 Waterloo St., London, Ont.

Clinical Pediatric Society of Israel

Chairman: Dr. I. Heyman, Hadassah Municipal Hospital, Tel-Aviv.
Committee: Dr. E. Schoenfeld, Tsahalon Government Hospital, Jaffa, Tel-Aviv, Dr. Bernard E. Cohen, Tel Hashomer Government Hospital, Tel Litwinski.
Place: Hospital Pediatric Services throughout country. Time: Bi-monthly.

Danish Pediatric Society

President: Dr. A. Rothe-Meyer, Children's Hospital, Fûglebakken, Copenhagen F.
Secretary: Dr. E. Winge Flensborg, Children's Hospital, Martinsvej, Copenhagen V.
Place: Different hospitals. Time: First Wednesday of every month.

Deusche Gesellschaft für Kinderheilkunde

President: Prof. Dr. med. W. Keller, Freiburg/Brsg., Universitäts-Kinderklinik.
President-Elect: Prof. Dr. med. K. Klinke, Dusseldorf, Kinderklinik d. Medizinischen Akademie, Moorenstr. 5.
Secretary: Prof. Dr. med. J. Jochims, Lubeck, Stadt. Kinderklinik, Kronsforder Allee 71/73.

*Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

GREEK PEDIATRIC ASSOCIATION

President: Dr. Spiros Bartsocas.
Honorary Secretary: Dr. Egle Inglessi, 4 Milioni St., Athenes.

ISRAEL PEDIATRIC SOCIETY

Chairman: Prof. Sh. Rosenbaum, 26 Bialik St., Tel Aviv.
Secretary: Dr. R. Kochmann, 131 Ben Jehuda Rd., Tel Aviv.
Place: Tel Aviv.

NEDERLANDSE VEREENIGING VOOR KINDERGENEESKUNDE

President: Dr. G. J. Huët, 39 Brediusweg, Bussum.
Secretary: Dr. H. Reerink, c/o Sophia Kinderziekenhuis, 160 Gordelweg, Rotterdam.
Place: Children's Hospital or Pediatric Clinic. Time: Three times a year.

NORSK PEDIATRISK SELSKAP

President: Dr. Henrik Hagelstein, Children's Department, Rikshospitalet, Oslo.
Secretary: Dr. Kare Havard Torp, Children's Department, Ullevål Hospital, Oslo.
Time: Friday, six times a year.

PAEDIATRIC SOCIETY OF VICTORIA

President: Dr. J. F. Williams, 12 Collins Street, Melbourne, Victoria.
Honorary Secretary: Dr. H. E. Williams, Royal Children's Hospital, Carlton, Victoria.
Place: Lecture Theatre of the Royal Children's Hospital.
Time: Second Wednesday in each month at 8:00 p.m.

PEDIATRIC SOCIETY OF NEW ZEALAND

President: Dr. Edward J. Cronin, Power Board Bldg., Queen St., Auckland.
Secretary: Dr. J. D. Matthews, 104 Symonds St., Auckland.

PHILIPPINE PEDIATRIC SOCIETY

President: Dr. Florencio N. Quintos.
Secretary-Treasurer: Dr. Lino Ed. Lim, Manila.
Place: Physician's Club, Dewey Blvd., Manila. Time: Every two months; last Thursday of September, November, January, and March.

ROYAL SOCIETY OF MEDICINE, SECTION OF PAEDIATRICS

President: G. H. Macnab, F.R.C.S.
Honorary Secretaries: Ursula James, M.R.C.P., and Leslie Scott, M.D.
Sectional Editor: D. MacCarthy, M.D.
Place: 1 Wimpole St., London W.1 (Correspondence for these honorary officers should be sent to this address). Time: Fourth Friday of each month, 4:15 p.m.

SCHWEIZERISCHE GESELLSCHAFT FÜR PÄDIATRIE

President: Prof. W. Tobler, Brunnadernrain 11, Bern.
Vice-President: Prof. M. Jaccottet, Av. de Rumine, Lausanne.
Secretary: Dr. J. Haas, Westl. Alpenstrasse 3, Burddorf.

SOCIEDAD ARGENTINA DE PEDIATRIE

President: Dr. Rudolfo Kreutzer.
Secretary: Dr. Luis M. Cucullu.
Place: Sante Fè 1178, Buenos Aires.

SOCIEDAD BOLIVIANA DE PEDIATRIA

President: Dr. Carlos Daza Meruvia.
Secretary: Dr. Cecilio Abela Deheza.
Place: S.C.I.S.P. Bldg. Time: Every Thursday.

SOCIEDAD CHIHUAHUENSE DE PEDIATRIA

President: Dr. Alfonso Ruiz Escalona.
Secretary: Dr. Armando G. Herrera.
Place: Hospital Infantil del Estado, Chihuahua, Chih., Mexico.

Sociedad Chilena de Pediatria

President: Prof. Dr. Raúl Gantes A.
Secretary-General: Dr. Edmundo Cardemil.
Place: Medical Society, Merced 565, Santiago.

Sociedad Colombiana de Pediatria

President: Dr. Alfonso Vargas Rubiano.
Vice-President: Dr. Darío Gutiérrez Laserna.
Secretary: Dr. Omar García Bustamante.
Treasurer: Dr. Alfonso Gutiérrez Reyes.

Sociedad Cubana de Pediatria (Filial Cienfuegos)

President: Dr. Rafael Viego Delgado.
Secretary: Dr. Ramon Azaret Moron, Santa Cruz No. 167, Cienfuegos, Cuba.
Place: Colegio Medico. Time: 9:00 p. m., Wednesdays, six times a year.

Sociedad Ecuatoriana de Pediatria (new listing)

President: Dr. Aldo Muggia.
Secretary: Dr. Nicolas Espinosa, Hospital Baca Ortiz, Quito, Ecuador, S. A.
Place: Hospital Baca Ortiz, Quito, Ecuador. Time: Monthly.

Sociedad de Pediatria de Concepcion (Chile)

President: Dr. Daniel Campos, Hospital Clínico Regional, Concepción.
Secretary: Dr. Obdulia Jiménez, Hospital Clínico Regional, Concepción.
Place: Hospital Clinico Regional Concepción. Time: 7:30 p. m., second Tuesday of every month, April to December, inclusive.

Sociedad de Pediatria del Litoral

President: Dr. Raul Bruera.
Vice-President: Dr. Isidoro Slullitel.
Secretary-General: Dr. Elsa Galimany.

Sociedad de Pediatria y Puericultura del Atlantico

President: Dr. Atilio Marino.
Vice-President: Dr. Helena Uribe de Jimenez.
Secretary-Treasurer: Dr. Hernando Barrios-Angulo.

Sociedade de Pediatria da Bahia

President: Dr. Elysio Pereira de Athayde.
Secretary: Dr. Eliezer Audiface.

Sociedade de Pediatria de Pernambuco

President: Dr. Antonio Aureliano.
Secretary: Dr. Claudia Figueiredo.

Sociedade de Pediatria do Rio Grande do Sul

President: Dr. Francisco Talaia de Moura.
Secretary: Dr. Enio Pilla.

Sociedade de Puericultura e Pediatria do Maranbao

President: Dr. Ordorico Amaral de Mattos.
Secretary: Dr. Joao Mohana.

Sociedade Mineira de Pediatria

President: Dr. Agostinho Fernandes.
Secretary: Dr. Celio Marques Scotti.

Sociedade Portugesa de Pediatria

President: Prof. Dr. Lucio de Almeida.
Vice-President: Dr. Cordeiro Ferreira.
Secretary-General: Prof. Dr. Carlos Salazar de Sousa.
Treasurer: Dr. Mario Cordeiro.
Place: Clinica pediatrica do Hospital D. Estefania, Lisbon. Time: Monthly.

SOCIEDAD URUGUAYA DE PEDIATRIA

President: Dr. Euclides Peluffo.
Secretary: Dr. Ruben Gorlero Bacigalupi.
Place: Av. Agraciada 1464, piso 13, Montevideo.

SOCIEDAD VENEZOLANA DE PUERICULTURA Y PEDIATRIA

President: Dr. Miguel Raga.
Vice-President: Dr. Jorge Lizarraga.
Secretary: Dr. Hernan Mendez C.

SOCIEDAD YUCATECA DE PEDIATRIA

President: Dr. Humberto Perez Concha.
Secretary: Dr. Prudencio Ruiz Salazar.
Treasurer: Dr. Jorge Antiveros Andrade.

LA SOCIETE DE PEDIATRIE DE MONTREAL

President: Dr. Remi Archambault.
Vice-President: Dr. Claude Leonard.
Secretary: Dr. Paul Dagenais-Perusse, La Societe de Pediatrie de Montreal, Inc., Montreal, Canada.

SOCIETE DE PEDIATRIE DE PARIS

President: Prof. Jean Cathala, 45 rue Scheffer, Paris XVI.
Secretary: Prof. Maurice Lamy, 94 rue de Varenne, Paris VII.
Place: Hôspital des Enfants Malades, 149 rue de Sèvres, Paris XV. Time: 4 p. m., third Tuesday of each month.

SOCIETE DE PEDIATRIE DE QUEBEC

President: Dr. Roland Thibaudeau, 203 des Erables, Québec.
Secretary: Dr. Euclide Dechêne, 312 du Roi, Québec.
Place: Quebec. Time: May and November.

SOCIETA ITALIANA DI PEDIATRIA

President: Prof. Giuseppe Caronia.
Vice-Presidents: Prof. Mario Cotellessa and Prof. Gaetano Salvioli.
Secretary: Prof. Rolando Bulgarelli.

SOUTH AFRICAN PAEDIATRIC ASSOCIATION

Chairman: Dr. H. L. Wallace, Durban.
Honorary Secretary-Treasurer: Dr. F. Walt, 126 Trust Building, Gardiner St., Durban.

SWEDISH ASSOCIATION OF PEDIATRICS

President: Prof. Sture Siwe, Lund.
Secretary: Dr. Karl-Axel Melin, Färjestadsvägen 16, Bromma.

SWEDISH MEDICAL SOCIETY, SECTION FOR PEDIATRICS AND SCHOOL HYGIENE

President: Docent Justus, Ström, Stockholm.
Secretary: Dr. M. d'Avignon, Pediatric Clinic, Karolinska Sjukhuset, Stockholm 60.
Place: Swedish Medical Society, Klara Östra Kyrkogata 10, Stockholm. Time: Second Friday of each month, except summer.

UNITED STATES

National

AMERICAN MEDICAL ASSOCIATION, SECTION ON PEDIATRICS

Chairman: Dr. M. G. Peterman, 411 E. Mason St., Milwaukee.
Secretary: Dr. Wyman C. C. Cole, 3001 W. Grand Blvd., Detroit.

AMERICAN ACADEMY OF PEDIATRICS

President: Dr. Edgar E. Martmer, 693 Washington Rd., Grosse Pointe 30, Mich.
Vice-President and President Elect: Dr. Stewart H. Clifford, 1101 Beacon Street, Brookline 46, Mass.

Executive Secretary and Treasurer: Dr. E. H. Christopherson, 1801 Hinman Ave., Evanston, Ill.
Place: Chicago, October, 1956.

Society for Pediatric Research

President: Dr. William Wallace, 2065 Adelbert Rd., Cleveland.
Vice-President: Dr. Harry Waisman, Madison, Wis.
Secretary-Treasurer, Dr. Sydney S. Gellis, Boston University School of Medicine, Boston.
Place: Carmel, California. Time: June 20-22.

The American Pediatric Society

President: Dr. Daniel C. Darrow, 5847 Howe Drive, Mission, Kan.
Vice-President: Dr. Samuel Z. Levine, 525 E. 68th Street, New York.
Secretary-Treasurer, Dr. Aims C. McGuinness, 8614 Montgomery Ave., Philadelphia.
Recorder-Editor: Dr. Stewart H. Clifford, 1101 Beacon Street, Brookline 46, Mass.
Place: Carmel, California. Time: June 17, 18, and 19, 1957.

Sectional

Intermountain Pediatrics Society

President: Dr. Stanley Childs, 2000 So. 9th East, Salt Lake City, Utah.
Vice-President: Dr. Hal Wakefield, Utah Valley Hospital, Provo, Utah.
Secretary: Dr. Robert S. Ely, 1940 So. 2nd East, Salt Lake City, Utah.
Place: Salt Lake City, Utah.

New England Pediatric Society

President: Dr. Edward T. Wakeman, 240 Bradley St., New Haven, Conn.
President-Elect: Dr. Allan M. Butler, Mass. General Hospital, Boston.
Secretary: Dr. Harry Shwachman, Childrens Hospital, Boston.
Place: Boston for three meetings and one in another North East city.
Time: October, December, March, and June.

North Pacific Pediatric Society

President: Dr. S. Gorham Babson, 1107 S. W. 13th, Portland 5, Ore.
President-Elect: Dr. Norman Murphy, Seattle, Wash.
Secretary: Dr. Peter Spohn, 3195 Granville Street, Vancouver, B. C.
Meeting: April, Seattle.

Northwestern Pediatric Society

President: Dr. A. J. Ouellette, 1530 Larpenteur Ave., St. Paul, Minn.
Vice-President: Dr. Elizabeth Lowry, 301 Kenwood Parkway, Minneapolis.
Secretary-Treasurer: Dr. T. C. Papermaster, 215 Doctors' Bldg., Minneapolis.

Rocky Mountain Pediatric Society

President: Dr. James Kennedy, 1447 Florence, Denver.
Vice-President: Dr. Leo J. Flax, 1575 Vine, Denver 6.
Secretary-Treasurer: Dr. Jules Amer, 1575 Vine, Denver 6.
Place: University Club, Denver.

Southwestern Pediatric Society

President: Dr. Thomas Harris, 436 N. Roxbury Drive, Beverly Hills, Calif.
Vice-President: Dr. Wendell Redfern, 125 E. Glenoaks Blvd., Glendale, Calif.
Secretary: Dr. Gordon Richardson, 10711 Riverside Drive, North Hollywood, Calif.
Place: University Club, Los Angeles, Calif. Time: September, November, January, and March.

Western Society for Pediatric Research

President: Dr. James F. Bosma, 1940 So. 2nd East, Salt Lake City, Utah.
Vice-President: Dr. Wm. Deamer, Dept. of Pediatrics, University of California, San Francisco.
Secretary: Dr. Robert H. Alway, Stanford School of Medicine, San Francisco.
Place: Salt Lake City, Utah.

State

Alabama Pediatric Society

President: Dr. David B. Monsky, 748 Adams St., Montgomery 5.
Secretary: Dr. Alice H. Pye, 305 Church St., Montgomery.
Place: Montgomery.

Arizona State Pediatric Society

President: Dr. B. P. Starts, 1018 N. Country Club Rd., Tucson.
Secretary: Dr. Jack H. Demlow, 130 S. Scott, Tuscon.
Time: Spring and Fall.

California Medical Association, Section on Pediatrics

Chairman: Dr. Moses Grossman, University of California Medical Center, San Francisco.
Secretary: Sidney Rosin, 6230 Wilshire Blvd., Los Angeles.

Florida State Pediatric Society

President: Dr. Wesley S. Nock, 273 Alhambra Circle, Coral Gables.
Vice-President: Dr. Joel V. McCall Jr., 111 Broadway, Daytona Beach.
Secretary-Treasurer: Dr. Henry G. Morton, 1950 Arlington Ave., Sarasota.

Georgia Pediatric Society

President: Dr. Frank Thomas, Albany.
Vice-President: Dr. Bessie Mae Beach, 309 Martin Bldg., Columbus.
Secretary: Dr. C. Dixon Fowler, 27 Eighth St., N. E., Atlanta.
Time: May.

Hezekiah Beardsley Pediatric Club of Connecticut

President: Dr. James M. Sturtevant, 358 Montauk Ave., New London, Conn.
Treasurer: Dr. Edward T. Wakeman, 240 Bradly St., New Haven, Conn.
Secretary: Dr. Robert P. Rogers, 90 Dayton Ave., Greenwich, Conn.

Illinois State Medical Society, Section on Pediatrics

Chairman: Noel G. Shaw, 636 Church St., Evanston.
Secretary: Raymond Eveloff, 1025 South 7th St., Springfield.

Indiana State Pediatric Society

President: Dr. Byron K. Rust, 3740 Central Avenue, Indianapolis.
Secretary: Dr. Wallace E. Bash, 2318 South Fairfield, Ft. Wayne.

Iowa Pediatric Society

President: Dr. James E. Dyson, 3200 University Avenue, Des Moines.
Vice-President: Dr. Maryelda Rockwell, 220 Tucker Bldg., Clinton.
Secretary: Dr. Ralph E. Dyson, 3200 University Avenue, Des Moines, Iowa
Place: Spring meeting in conjunction with the Iowa State Medical Society meeting. Fall meeting in Sept. at University Hosp., Iowa City.

Kansas State Pediatric Society

President: Dr. David R. Davis, Emporia.
Vice-President: Dr. C. T. Hinshaw, Wichita.
Secretary: Dr. Theodore Young, 103½ East Ninth St., Winfield.
Place: Broadview Hotel, Emporia.

Kentucky Pediatric Society

President: Dr. Alexander J. Alexander, 109 Esplanade, Lexington.
Secretary: Dr. Robert B. Warfield, 180 Market Street, Lexington.
Place: Lexington, Kentucky. Time: Spring, 1957.

Louisiana State Pediatric Society

President: Dr. Suzanne Schaefer, 3439 Prytania St., New Orleans.
Vice-President: Dr. Conway S. Magee, Gordon Bldg., Lake Charles.
Secretary: Dr. Joseph M. Perret, Jr., 2329 S. Carrollton, New Orleans.
Place: New Orleans. Time: Spring, 1957.

Michigan State Medical Society, Pediatric Section

President: Dr. Harry A. Towsley, University Hospital, 1313 Ann St., Ann Arbor.
Secretary: Dr. Charles Frank Payton, 611 S. Washington, Royal Oak.

Montana Pediatric Society

President: Dr. George W. Nelson, Billings.
Vice-President: Dr. Joseph W. Brinkley, Great Falls.
Secretary: Dr. Frank J. Friden, Great Falls.
Time: Twice yearly, usually March and September.

Nebraska Pediatric Society

President: Dr. E. S. Wegner, 724 Sharp Building, Lincoln.
Vice-President: Dr. Robert Grant, 909 Sharp Bldg., Lincoln.
Secretary: Dr. Gilbert Schreiner, 125 No. 38th St., Omaha.
Place: Omaha. Time: Third Thursday of each month at the Childrens Memorial Hospital, Omaha.

New Hampshire Pediatric Society

President: Dr. Arthur Laidlaw, Keen.
Secretary-Treasurer: Dr. Robert F. Wilson, 113 Locust St., Dover.
Place: Concord, Manchester, Dover, Hanover.

New Mexico Pediatric Society

President: Dr. Albert S. Lathrop, P. O. Box 912, Coronado Bldg., Santa Fe.
Vice-President: Dr. Guy E. Rader, 4120 Silver S. E., Albuquerque.
Secretary: Dr. Carol K. Smith, P. O. Box 2056, Coronado Bldg., Santa Fe.
Place: Variable. Time: Four times a year.

North Carolina Pediatric Society

President: Dr. Charles F. Williams, 817 Hillsboro St., Raleigh.
Vice-President: Dr. George A. Watson, 306 S. Gregson St., Durham.
Secretary: Dr. Bailey Webb, 809 W. Chapel Hill St., Durham.

South Carolina Pediatric Society

President: Dr. William R. Deloache, 13 Medical Court, Greenville.
Vice-President: Dr. Fred F. Adams, 157 Pine St., Spartanburg.
Secretary: Dr. Guy C. Castles Jr., 1417 Gregg St., Columbia.

Tennessee Pediatric Society

President: Dr. Thomas Fort Bridges, 1814 Hayes St., Nashville.
Vice-President: Dr. William G. Crook, 648 W. Forest St., Jackson.
Secretary: Dr. Stewart Smith, 605 Lindsay St., Chattanooga.
Place: Nashville. Time: April 8-9, 1957.

Texas Pediatric Society

President: Dr. Russell J. Blattner, Baylor Medical College, Houston.
President-Elect: Dr. E. M. Wier, 1216 Pennsylvania, Fort Worth.
Secretary: Dr. James N. Walker, 5216 W. Freeway, Fort Worth.

Virginia Pediatric Society

President: Dr. T. S. Chalkley, 3011 Monument Ave., Richmond.
Vice-President: Dr. A. P. Booker, 1021 West Main St., Charlottesville.
Secretary-Treasurer: Dr. Harry L. Cox, 113 Fauquier St., Portsmouth.
Place: Williamsburg. Time: March 22 and 23, 1957.

Wisconsin State Medical Society, Section of Pediatrics

Chairman: Dr. E. H. Pawsat, Fond du Lac.
Vice-Chairman: Dr. Samuel E. Kohn, Milwaukee.
Secretary: Dr. J. R. Schroder, Janesville.
Delegate: Dr. K. J. Winters, Wauwatosa.
Alternate Delegate: Dr. F. Mellencamp, Milwaukee.

Local

Academy of Medicine of Cleveland, Pediatric Section

Chairman: Dr. C. T. J. Dodge, 15457 Euclid Ave., Cleveland 12.
Secretary: Dr. Beulah Wells, 10515 Carnegie Ave., Cleveland 6.
Place: Allen Memorial Medical Library. Time: 8:15 p.m., October, December, February, and March.

Akron Pediatric Society

President: Dr. Lewis E. Rector, 410 Akron Savings and Loan Bldg.
Vice-President: Dr. Noah Miller, 193 West Market St.
Secretary: Dr. Walter W. Lang, 154 N. Water St., Kent, Ohio.

Baltimore City Medical Society, Pediatric Section

President: Dr. S. Shipley Glick, 3914 Park Heights Ave., Baltimore.
Vice-President: Dr. Melchijah Spragens, 102 Alleghany Ave., Baltimore.
Secretary: Dr. Harry H. Gordon, Sinai Hospital of Baltimore, Inc.
Place: 1211 Cathedral St., Baltimore. Time: Second Tuesday in November, January, and March at 8:30 p.m.

Bronx Pediatric Society

President: Dr. Leon Greenspan, 239 Mount Hope Place, New York.
Vice-President: Dr. Harold H. Aaron, 647 W. 207 St., New York.
Secretary-Treasurer: Dr. Jess Diamond, 1900 Grand Concourse, New York.
Place: Morrisania City Hospital. Time: 8:30 p.m., second Wednesday of each month, except June, July, August, and September.

Brooklyn Academy of Pediatrics

President: Dr. Henry Cohen, 1761 E. 19th St.
Vice-President: Dr. J. Philip Lombard, 115 Woodruff Avenue.
Secretary: Dr. Adolph H. Emerson, 7721 Ridge Blvd.
Place: Granada Hotel. Time: Fourth Wednesday of February, March, April, October, and November at 8:00 p.m.

Buffalo Pediatric Society

President: Dr. Norman C. Bender, 227 Colvin Ave.
Vice-President: Dr. Thomas S. Bumbalo, 354 Lincoln Parkway.
Secretary-Treasurer: Dr. Lois J. Plummer, 131 Linwood Ave.

Central Illinois Pediatrics Society

President: Dr. Carl E. Sibilsky, 815 First National Bank Bldg., Peoria.
Vice-President: Dr. O. E. Ehrhardt, 1321 South Fourth St., Springfield.
Secretary: Dr. Richard E. Dukes, Carle Clinic, Urbana.
Time: April, 1957.

Central New York Pediatric Club

President: Dr. Paul W. Beaven, 20 N. Goodman St., Rochester.
Vice-President: Dr. Howard A. Gilmartin, Schenectady.
Secretary: Dr. Fred W. Bush, 325 Park Ave., Rochester.
Time: Twice Yearly.

Central Ohio Pediatric Society

President: Dr. Miner W. Seymour, 375 E. Town St., Columbus.
Secretary: Dr. William E. Baldock, 4150 Indianola Ave., Columbus.

Chicago Pediatric Society

President: Dr. S. C. Henn, 2376 E. 71st St.
Vice-President: Dr. Ralph H. Kunstadter, 664 N. Michigan Ave.
Secretary: Dr. Raymond Grissom, 715 Lake St., Oak Park, Ill.

Cincinnati Pediatric Society

President: Dr. William D. De Vaux, 7373 Brookcrest Dr.
Vice-President: Dr. Daniel V. Jones, 7373 Brookcrest Dr.

Secretary: Dr. Harold A. Cassady, 2728 Erie Ave.
Place: Research Library, Children's Hospital. Time: On call.

Cleveland Academy of Medicine, Pediatric Section

Chairman: Dr. Robert Hauver, 10515 Carnegie Ave.
Secretary: Dr. William Herman, 10300 Carnegie Ave.

Corpus Christi Pediatric Society

President: Dr. Jack F. McKemie, 527 Gordon.
Vice-President: Dr. Hannah B. Woody, 515 Elizabeth.
Secretary: Dr. Jos. Oshman, 1010 Ohio.

Dallas Pediatric Society

President: Dr. Floyd A. Norman, 4325 Cole Ave., Dallas.
Secretary-Treasurer: Dr. Charles L. Smith, 4207 Lemmon Ave., Dallas.
Place: Children's Hospital of Texas. Time: 6:30 p.m., first Thursday in each month.

Detroit Pediatric Society

President: Dr. Glen E. Hause, 18520 Grand River.
President-Elect: Dr. Louis E. Heideman, 20211 Greenfield.
Secretary: Dr. Charles G. Jennings, 14827 E. Jefferson.
Treasurer: Dr. Douglas Wake, 1307 S. Washington, Royal Oak.
Permanent Mailing Address: 5224 St. Antoine (2).

Fort Worth Pediatric Society

President: Dr. Randall Nyman, 1015 Pennsylvania.
Secretary: Dr. James Hooher, 1111 Pennsylvania.
Place: Variable. Time: 6:30 p.m., third Friday of each month.

Honolulu Pediatric Society

President: Dr. Douglas Murray.
Secretary: Dr. Duke Cho Choy, 1010 S. King Street.
Place: Homes of members. Time: Third Thursday of each month.

Houston Pediatric Society

President: Dr. R. E. Leaton, 3102 San Jacinto.
Vice-President: Dr. M. Eleanor Blish, 4705 Montrose.
Secretary: Dr. Elizabeth Bratteng, 1729 Sunset.
Place: Announced. Time: Fourth Tuesday of January, March, May, July, September and November.

Kansas City Southwest Pediatric Society

President: Dr. Frank Houge, Plaza Medical Bldg., Kansas City, Mo.
Secretary: Dr. S. J. Kranson, Truman Rd. and Ash, Independence, Mo.
Place: University Club, Kansas City, Mo. Time: On call.

Long Beach Pediatric Society

President: Dr. Kenneth Berkaw, 211 Cherry Ave., Long Beach, Calif.
Secretary: Dr. C. W. Latshaw, 3821 Atlantic Ave., Long Beach, Calif.
Place: Victor Hugo Restaurant, 730 E. Broadway. Time: First Tuesday night of every month.

Los Angeles County Medical Association, Pediatric Section

President: Dr. Robert F. Chinnock.
Vice-President: Dr. Margaret H. Jones.
Secretary-Treasurer: Dr. Morris J. Naiditch, 239 S. La Cienega Blvd., Beverly Hills, Calif.

Louisville Pediatric Society

President: Dr. Owen S. Ogden, Fincastle Bldg.
Vice-President: Dr. J. J. Glaboff.
Secretary-Treasurer: Dr. Jos. W. Fowler.
Place: Variable. Time: Five times a year, as announced.

Medical Society of the County of Kings and Academy of Medicine of Brooklyn, Pediatric Section

President: Dr. Joseph B. Pincus, 881 Washington Ave., Brooklyn.
Vice-President: Dr. Arthur L. Ruby, 1331 E. 19th St., Brooklyn.
Secretary: Dr. David Dragutsky, 1466 - 49th St., Brooklyn.
Treasurer: Dr. Abraham Gilner, 1328 - 49th Street, Brooklyn.

Medical Society of the District of Columbia, Section on Pediatrics

President: Dr. George Maksim, 1418 Good Hope Rd. S. E., Washington, D. C.
Vice-President: Dr. Wm. A. Howard, 1517 30th St. N. W., Washington, D. C.
Secretary: Dr. John E. Cassidy, 9911 Old Georgetown Rd., Bethesda, Md.

Memphis Pediatric Society

President: Dr. Price Stepp, 848 Adams, Memphis, Tenn.
Vice-President: Dr. W. R. Graves, 505 South Highland, Memphis, Tenn.
Secretary: Dr. Robert G. Jordan, 848 Adams, Memphis, Tenn.
Place: Rotated among four hospitals. Time: 7:30 p.m., second Tuesday each month.

Milwaukee Pediatric Society

President: Dr. Vernon Kores, 6040 W. Lisbon Ave., Milwaukee.
Vice-President: Dr. Karl Beck, 1411 Wauwautosa Ave., Milwaukee.
Secretary: Dr. Paul S. Pierson, 1513 E. Capitol Drive, Milwaukee.
Place: University Club. Time: Quarterly.

Mobile Pediatric Society

President: Dr. Daniel Sullivan, 1420 Government St., Mobile, Ala.
Secretary: Dr. Robert O. Harris III, 1514 Government St., Mobile, Ala.
Place: Admiral Semmes Hotel. Time: 7:30 p.m., fourth Thursday of September, November, January, March, and May.

Nashville Pediatric Society

President: Dr. Ethel Walker 2509 West End Avenue, Nashville 5, Tenn.
Secretary: Dr. Richard P. Taber, 2801 Gallatin Rd., Nashville 6, Tenn.
Place: Homes of members. Time: Third Thursday of each month.

Nassau Pediatric Society

President: Dr. Ralph Burns, Glen Cove, N. Y.
Vice-President: Dr. Virginia Lent, Hempstead, N. Y.
Secretary-Treasurer: Dr. David J. Posner, 98 Wolcott Road, Levittown, N. Y.
Place: Felice's Restaurant, Westbury, Long Island. Time: 7:30 p.m., second Monday of February, April, June, October, and December.

New York Academy of Medicine, Section on Pediatrics

Chairman: Dr. Benjamin Kramer, 60 Plaza St., Brooklyn.
Secretary: Dr. Henry L. Barnett, 535 East 68th St., New York.
Place: New York Academy of Medicine, 2 E. 103rd St., New York.
Time: 8:30 p.m., every second Thursday of October through May.

Northern California Pediatric Society

President: Dr. E. Revere Cole, 2901 Capitol Avenue, Sacramento 16, Calif.
Vice-President: Dr. Hubert Long, 2320 Channing Way, Berkeley 4, Calif.
Secretary: Dr. Samuel Hurwitz, 6200 Geary Blvd., San Francisco 21, Calif.
Place: St. Francis Hotel, San Francisco. Time: Quarterly as called.

Northern Ohio Pediatric Society

President: Dr. Chauncey W. Wyckoff.
President-Elect: Dr. William M. Champion.
Secretary-Treasurer: Dr. James B. Stewart, Babies and Childrens Hospital, 2103 Adelbert Road, Cleveland.

Oklahoma City Pediatric Society

President: Dr. Charles L. Freed, 430 N. W. 12th St., Oklahoma City, Okla.
Secretary: Dr. Jerome D. Shaffer, 1200 North Walker, Oklahoma City, Okla.
Place: Varies. Time: On Call.

Philadelphia Pediatric Society

President: Dr. Elizabeth Kirk Rose, 426 Owen Rd., Wynnewood, Pa.
Secretary: Dr. Robert H. High, 316 Simms St., Philadelphia 16.
Place: College of Physicians, 19 S. 22d St. Time: 8:30 p.m., second Tuesday from October to May, inclusive.

Pittsburgh Pediatric Society

President: Dr. W. W. Briant, Jr., 633 Washington Road.
Vice-President: Dr. R. R. Macdonald, 448 Brownsville Road.
Secretary: Dr. B. I. Michaels, 3500 5th Ave.
Place: Varies. Time: October, December, February, and April

Queens Pediatric Society

President: Dr. John L. Finnegan, 36-19 Bowne St., Flushing, N. Y.
Vice-President: Dr. Abram S. Tepper, 1225 Beach 12th St., Far Rockaway, N. Y.
Secretary: Dr. Benjamin Goldsmith, 40-27 Murray St., Flushing, N. Y.
Place: Seminole Club, Forest Hills, N. Y.

Richmond Pediatric Society

President: Dr. Hobart T. Dougan, 1832 Monument Ave., Richmond 20, Va.
Secretary: Dr. Robert A. Hoffman, 1001 W. Franklin St., Richmond 20, Va.
Place: Medical College Hospital. Time: 8 p.m., third Thursday of each month, except June, July, and August.

St. Louis Pediatric Society

President: Dr. Alfred S. Schwartz.
Vice-President: Dr. James P. King.
Secretary: Dr. Mirriam H. M. Pennoyer, 500 S. Kingshighway Blvd.
Place: Medart's Restaurant. Time: 7 p.m., second Thursday of each month from September to May, inclusive.

San Antonio Pediatric Society

President: Dr. Virginia Stovall, South Texas Building, San Antonio, Texas.
Vice-President: Dr. Ben Shaver, Medical Arts Building, San Antonio, Texas.
Secretary: Dr. C. Scott Stewart, 123 Ogden Lane, San Antonio, Texas.
Place: Bexar County Medical Library. Time: 7:00 p.m., first Tuesday of each month.

Santa Barbara Pediatric Society

President: Dr. Clarence B. Hills, 22B. W. Micheltorena St., Santa Barbara, Calif.
Secretary: Dr. Louise P. Brown, 3017 Foothill Rd., Santa Barbara, Calif.
Place: Varies. Time: Two to three times yearly, on call.

Seattle Pediatric Society

President: Dr. O. William Anderson.
President-Elect: Dr. Robert Tidwell.
Secretary-Treasurer: Dr. James L. Tucker.
Place: College Club. Time: 6:30 p.m., fourth Friday of each month from September to June.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Robert Trimby, Lansing, Mich.
Secretary: Dr. George H. Lowrey, University Hospital, Ann Arbor, Mich.
Place: University Hospital, Ann Arbor. Time: Yearly as announced.

Waco Pediatric Society

President: Dr. M. C. Carlisle, 1410 Austin Ave.
Secretary: Dr. A. O. Manske.
Place: 1918 Austin Ave., Waco, Texas. Time: Third Tuesday of each month.

Westchester County Medical Society, Pediatric Section

Chairman: Dr. Elvira Ostlund, 64 Highland Rd., Rye, N. Y.
Secretary: Dr. Irving Nelson, 150 E. Hartsdale Ave., Hartsdale, N. Y.
Place: Various hotels and clubs in the County. Time: Four meetings yearly—November, February, April, and June.

WESTERN MICHIGAN PEDIATRICS SOCIETY

President: Dr. John W. Thompson, 833 Lake Drive, S. E., Grand Rapids.
Vice-President: Dr. Ethon L. Stone, 721 - 17th St., Jackson.
Secretary: Dr. Donald C. Johns, 655 Broadview S. E., Grand Rapids.
Place: Grand Rapids in November and March. Other west Michigan cities in September and June.

WICHITA PEDIATRIC SOCIETY

President: Dr. Mary Blood.
Secretary: Dr. R. A. Nelson.
Place: Homes of members. Time: 8:30 p.m., first Thursday, October through May.

News and Comment

ANNOUNCEMENTS

Symposium on Fundamental Cancer Research.—The 11th Annual M. D. Anderson Hospital and Tumor Institute Symposium on Fundamental Cancer Research will be held March 7, 8, and 9, 1957, at The University of Texas M. D. Anderson Hospital and Tumor Institute in the Texas Medical Center, Houston.

The general topic for the symposium is "Viruses and Tumor Growth."

The first day of the symposium (Thursday, March 7) will consist of open house to all symposium members, and presentation of annual progress reports on certain current research projects will be made by the principal investigators of M. D. Anderson Hospital.

Friday, March 8, after an introduction by Dr. R. Lee Clark Jr., Director and Surgeon-in-Chief of the hospital, the presentation of the papers on viruses and tumor growth will begin, with Dr. Albert B. Sabin, The Children's Hospital Research Foundation, Department of Pediatrics, College of Medicine, University of Cincinnati, as chairman of the morning session.

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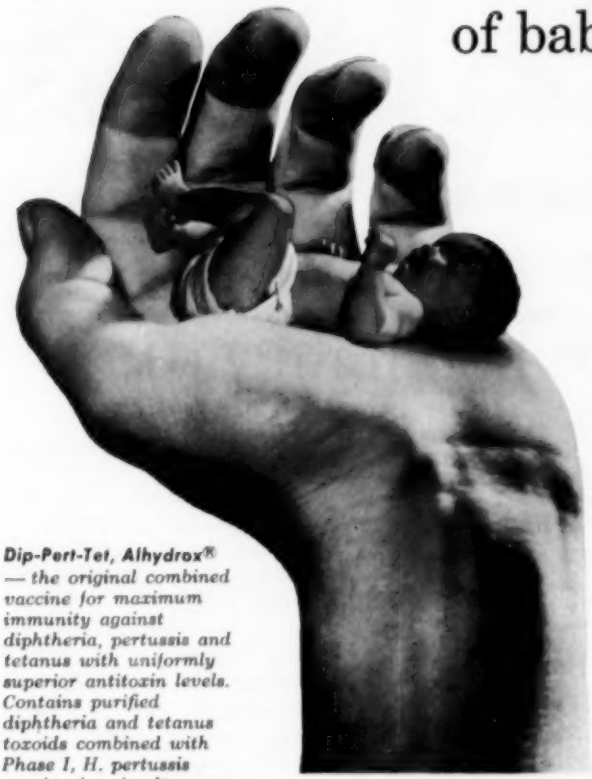

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These are some of the reasons why the role of enriched bread, in improving the health of millions of American school children, has been referred to as one of the most important advancements in public health measures since compulsory pasteurization of milk.

1. Martin, E.A.: Roberts' Nutrition Work with Children, Chicago, University of Chicago Press, 1954, p. 53.
2. Sebrell, W.H.: Developing Modern Nutrition Programs, Public Health Reports, United States Department of Health, Education and Welfare 69:277 (Mar.) 1954.
3. Joint Report of the Council on Dental Health and the Council on Dental Therapeutics of the American Dental Association: Sugar and Dental Caries: The Effect on the Teeth of Sweetened Beverages and Other Sugar-Containing Substances, J. Am. Dent. A. 47:387 (Oct.) 1953.

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*Shwachman, H., Children's Hospital, Boston; The Child in Health and Disease, Grulee and Eley, 2nd Edit.

Butler, A., Harvard Medical School, private communication.

Kagan, B., Ill. Med. Jl. 107; 120, (1955).

Gibbs, G. E., Bradley, J. E., and Minor, J. V., Diagnosis and Treatment of Cystic Fibrosis of the Pancreas. J.A.M.A. 145: 1187 (1951).

Everson, T. C., Grossman, M. I., and Ivy, A. C.: Bulletin of Amer. College of Surgeons, January, 1950.

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1. Merrill, A.L., and Watt, B.K.: Energy Value of Foods...Basis and Derivation, United States Department of Agriculture, Human Nutrition Research Branch, Agricultural Research Service. Agriculture Handbook No. 74, March 1955, pp. 8, 9, 25, 32-43, 60-87.
2. McCance, R.A., and Glaser, E.M.: The Energy Value of Oatmeal and the Digestibility and Absorption of Its Proteins, Fats and Calcium, Brit. J. Nutrition 2:221 (1948).
3. McLester, J.S., and Darby, W.J.: Nutrition and Diet in Health and Disease, ed. 6, Philadelphia, W.B. Saunders Company, 1952, pp. 189-190.

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References: (1) Millen, R.S.: N.Y. State J. Med. 55:779, 1955.
(2) Karpovitch, P.: Adventures in Artificial Respiration. New York, Associated Press, 1953.
(3) Eve, F. C.: Lancet 2:995 (1932); Eve, F. C., and Forsyth, H. C.: Brit. M. J. 2:584 (1948).
(4) Millen, R. S., Rowsom, A. F., and Mayberger, H. W.: Am. J. Obs. & Gyn. 70:1087, 1955.

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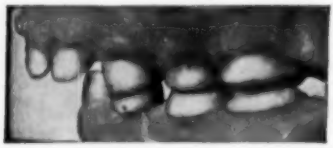

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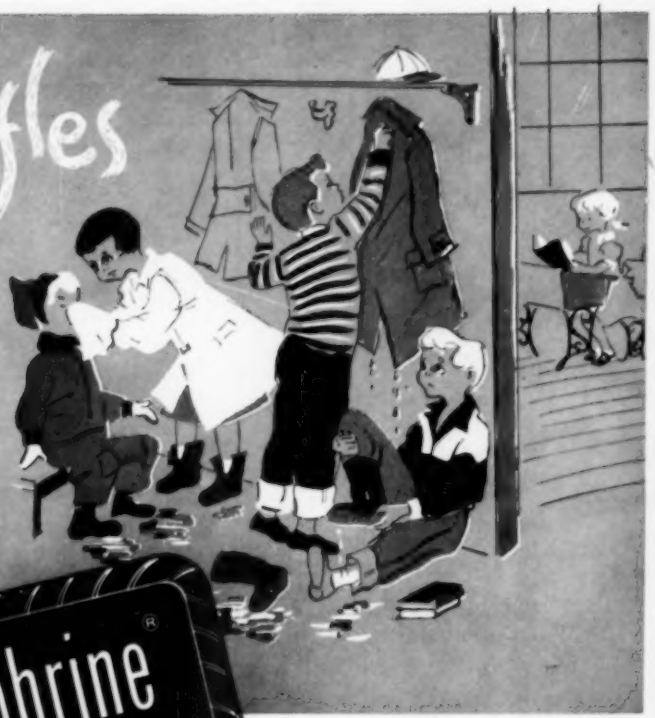

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